09/ 869,360

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PASSWORD:
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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 09  JAPIO to be reloaded August 25, 2002
 NEWS 20  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 21  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 22  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 23  Aug 26  Sequence searching in REGISTRY enhanced

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)
```

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:56:42 ON 02 SEP 2002

```
=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 16:56:52 ON 02 SEP 2002
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STRUCTURE FILE UPDATES:     1 SEP 2002  HIGHEST RN 446010-91-9
DICTIONARY FILE UPDATES:    1 SEP 2002  HIGHEST RN 446010-91-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09869360.str

L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR
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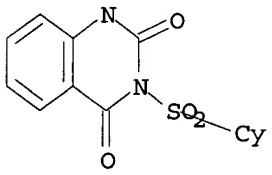


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Structure attributes must be viewed using STN Express query preparation.


=> s l1
SAMPLE SEARCH INITIATED 16:57:15 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     57 TO ITERATE

100.0% PROCESSED      57 ITERATIONS                                19 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          688 TO     1592
PROJECTED ANSWERS:             119 TO      641

L2           19 SEA SSS SAM L1

=> s l1 ful
FULL SEARCH INITIATED 16:57:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    938 TO ITERATE
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09/ 869,360

100.0% PROCESSED 938 ITERATIONS 218 ANSWERS
SEARCH TIME: 00.00.01

L3 218 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 140.28 140.49

FILE 'CAPLUS' ENTERED AT 16:57:28 ON 02 SEP 2002
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FILE COVERS 1907 - 2 Sep 2002 VOL 137 ISS 10
FILE LAST UPDATED: 1 Sep 2002 (20020901/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s chymase and inhibitor?
849 CHYMASE
783526 INHIBITOR?
L4 385 CHYMASE AND INHIBITOR?

=> s vascular or lipid or blood
104581 VASCULAR
213493 LIPID
987733 BLOOD
L5 1203367 VASCULAR OR LIPID OR BLOOD

=> s arteriosclerosis or coronary or angioplasty or claudication
9037 ARTERIOSCLEROSIS
45634 CORONARY
3416 ANGIOPLASTY
350 CLAUDICATION
L6 55122 ARTERIOSCLEROSIS OR CORONARY OR ANGIOPLASTY OR CLAUDICATION

=> s (cerebral infarction) or aneurysm or gangrene or hypertension
73534 CEREBRAL
20987 INFARCTION
1187 CEREBRAL INFARCTION
(CEREBRAL(W)INFARCTION)
927 ANEURYSM
733 GANGRENE
57062 HYPERTENSION

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```
L7       59714 (CEREBRAL INFARCTION) OR ANEURYSM OR GANGRENE OR HYPERTENSION

=> s renal infarction
         115877 RENAL
          20987 INFARCTION
L8           51 RENAL INFARCTION
                (RENAL(W)INFARCTION)

=> s l5 or l6 or l7 or l8
L9      1249143 L5 OR L6 OR L7 OR L8

=> s l4 and l9
L10         120 L4 AND L9

=> d his

     (FILE 'HOME' ENTERED AT 16:56:42 ON 02 SEP 2002)

     FILE 'REGISTRY' ENTERED AT 16:56:52 ON 02 SEP 2002
L1               STRUCTURE UPLOADED
L2            19 S L1
L3           218 S L1 FUL

     FILE 'CAPLUS' ENTERED AT 16:57:28 ON 02 SEP 2002
L4           385 S CHYMASE AND INHIBITOR?
L5       1203367 S VASCULAR OR LIPID OR BLOOD
L6         55122 S ARTERIOSCLEROSIS OR CORONARY OR ANGIOPLASTY OR CLAUDICATION
L7         59714 S (CEREBRAL INFARCTION) OR ANEURYSM OR GANGRENE OR HYPERTENSION
L8            51 S RENAL INFARCTION
L9       1249143 S L5 OR L6 OR L7 OR L8
L10          120 S L4 AND L9

=> s l3
L11            8 L3

=> d l11 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L11  ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:635930  CAPLUS
DOCUMENT NUMBER:          135:205544
TITLE:                    Preventive or therapeutic drugs for dermatitises
                          containing chymase inhibitors as the active ingredient
INVENTOR(S):              Fukami, Harukazu; Tomimori, Yoshiaki; Fukuda,
                          Yoshiaki; Watanabe, Naohiro
PATENT ASSIGNEE(S):       Suntory Limited, Japan
SOURCE:                   PCT Int. Appl., 123 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE           APPLICATION NO.  DATE
     ------------------  ----  --------       ---------------  --------
     WO 2001062294        A1   20010830       WO 2001-JP1323   20010222
         W:  AU, CA, CN, HU, JP, KR, US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, TR
     EP 1192950           A1   20020403       EP 2001-906226   20010222
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.:                  JP 2000-50504    A  20000222
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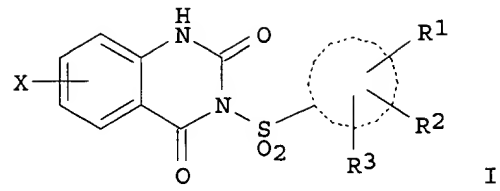
WO 2001-JP1323 W 20010222

GI



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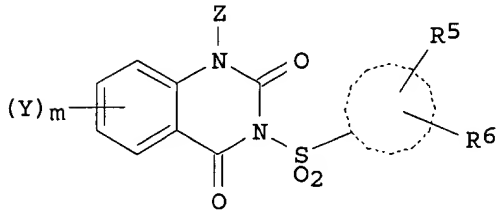


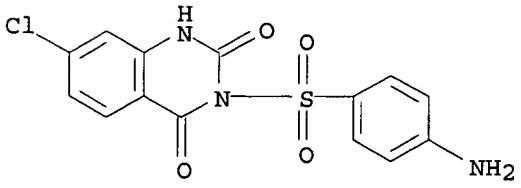
II

AB Preventive or therapeutic drugs for dermatitises accompanied with dimorphic inflammatory reactions and those caused by repeated exposure to antigens, which inhibit the progression of such dermatitises and are so safe by virtue of their being free from adverse effects as to bring about enhancement in the quality of daily life of a patient. Specifically, remedies for the above dermatitises contg. chymase inhibitors as the active ingredient, wherein the chymase inhibitors are quinazoline derivs. of the general formula (I) or (II) or pharmacol. acceptable salts thereof.

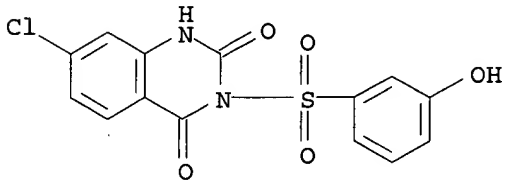
IT **189062-66-6P 259536-59-9P 259536-60-2P**
259536-61-3P 259536-62-4P 259536-63-5P
259536-64-6P 259536-65-7P 259536-66-8P
259536-67-9P 259536-68-0P 259536-69-1P
259536-70-4P 259536-71-5P 259536-72-6P
259536-73-7P 259536-74-8P 259536-75-9P
259536-76-0P 259536-77-1P 259536-78-2P
259536-79-3P 259536-80-6P 259536-81-7P
259536-82-8P 259536-83-9P 259536-84-0P
259536-85-1P 259536-86-2P 259536-87-3P
259536-88-4P 259536-89-5P 259536-90-8P
259536-91-9P 357423-99-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preventive or therapeutic drugs for dermatitises contg. chymase inhibitors as the active ingredient)

RN 189062-66-6 CAPLUS

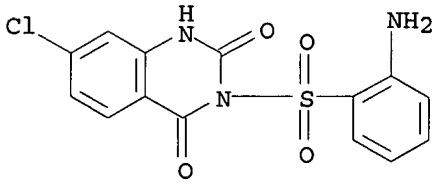
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



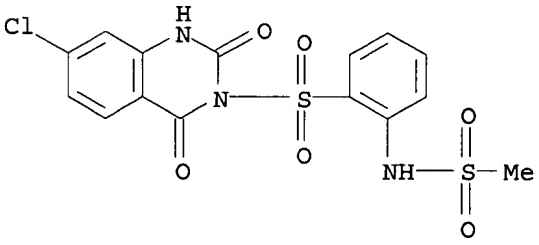
RN 259536-59-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



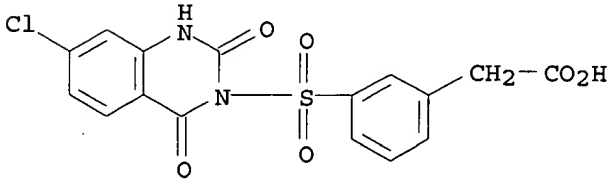
RN 259536-60-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(2-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



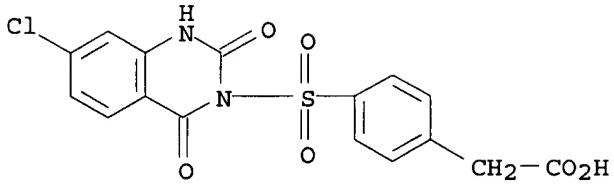
RN 259536-61-3 CAPLUS
CN Methanesulfonamide, N-[2-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



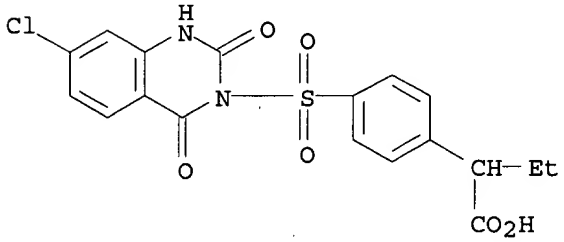
RN 259536-62-4 CAPLUS
CN Benzeneacetic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



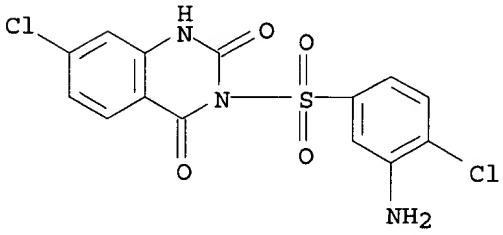
RN 259536-63-5 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



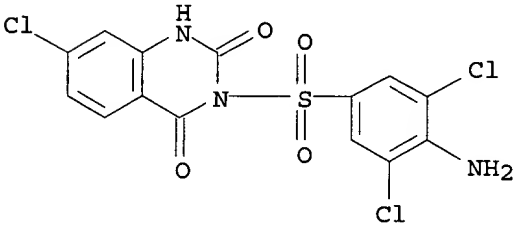
RN 259536-64-6 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl- (9CI) (CA INDEX NAME)



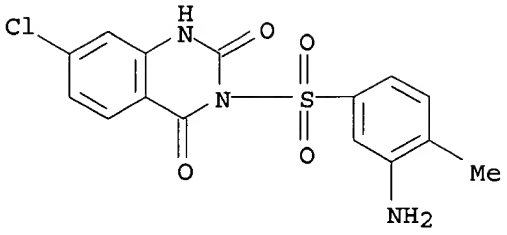
RN 259536-65-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-chlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



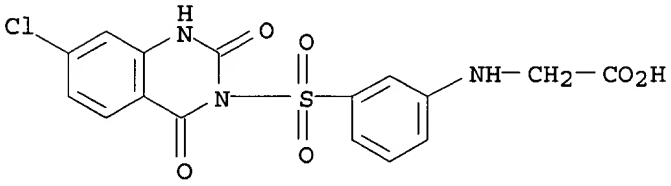
RN 259536-66-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-amino-3,5-dichlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



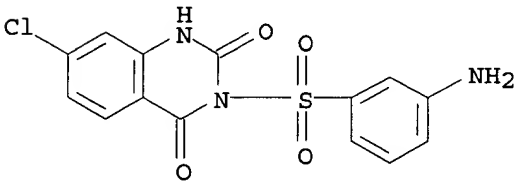
RN 259536-67-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



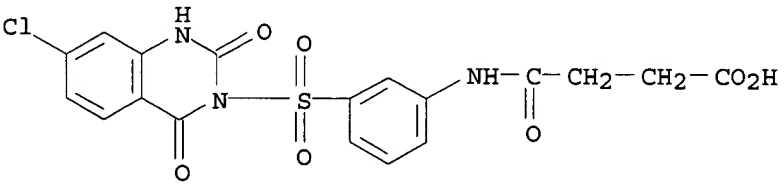
RN 259536-68-0 CAPLUS
CN Glycine, N-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



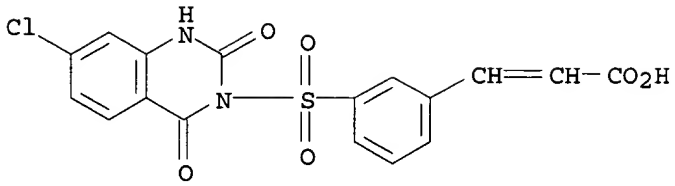
RN 259536-69-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



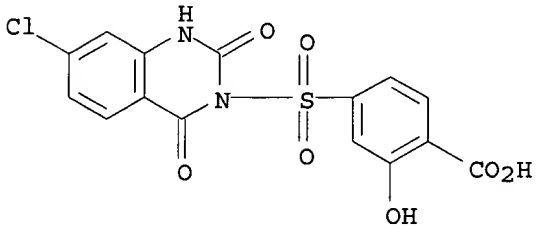
RN 259536-70-4 CAPLUS
CN Butanoic acid, 4-[[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]amino]-4-oxo- (9CI) (CA INDEX NAME)



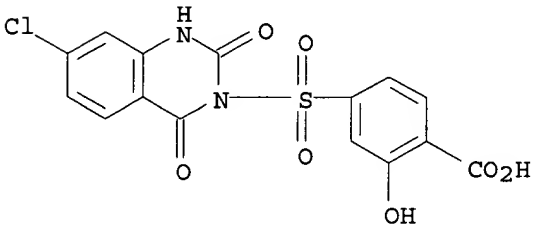
RN 259536-71-5 CAPLUS
CN 2-Propenoic acid, 3-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 259536-72-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)

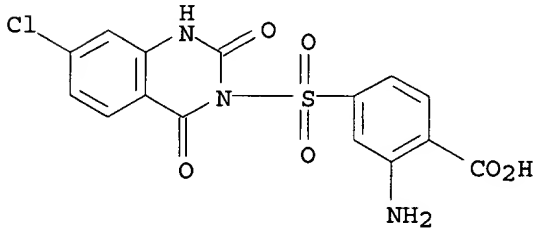


RN 259536-73-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy-, monosodium salt (9CI) (CA INDEX NAME)

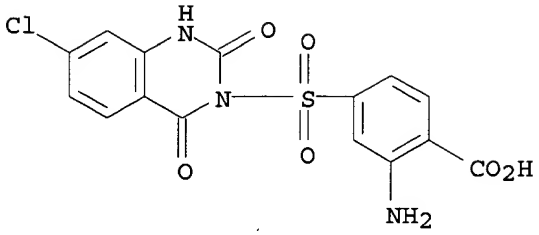


● Na

RN 259536-74-8 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)

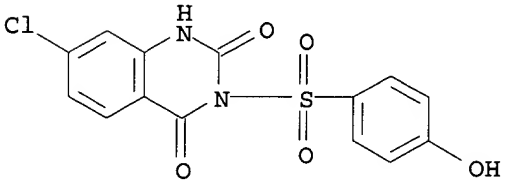


RN 259536-75-9 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)

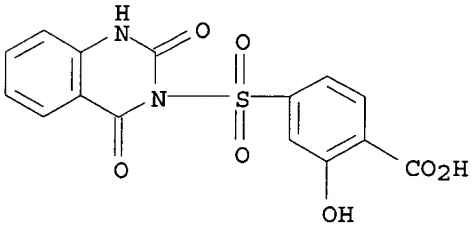


● Na

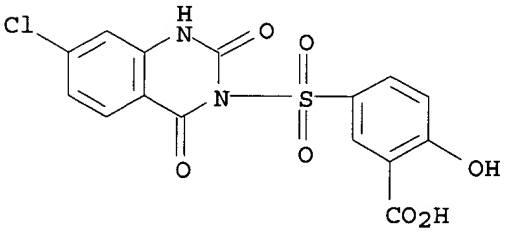
RN 259536-76-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



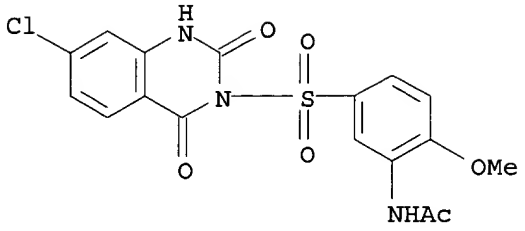
RN 259536-77-1 CAPLUS
CN Benzoic acid, 4-[(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



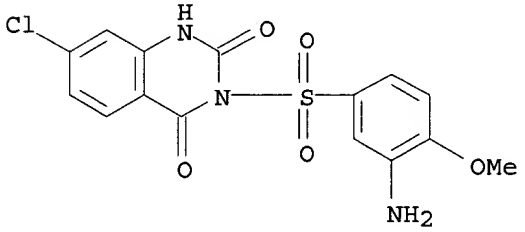
RN 259536-78-2 CAPLUS
CN Benzoic acid, 5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



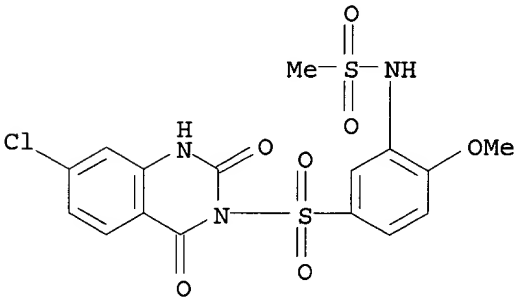
RN 259536-79-3 CAPLUS
CN Acetamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



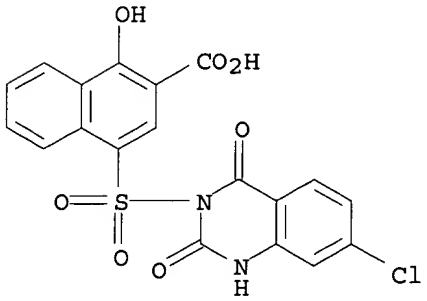
RN 259536-80-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methoxyphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



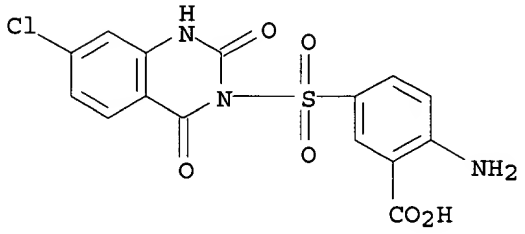
RN 259536-81-7 CAPLUS
CN Methanesulfonamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



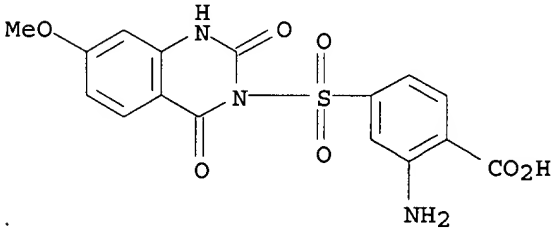
RN 259536-82-8 CAPLUS
CN 2-Naphthalenecarboxylic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1-hydroxy- (9CI) (CA INDEX NAME)



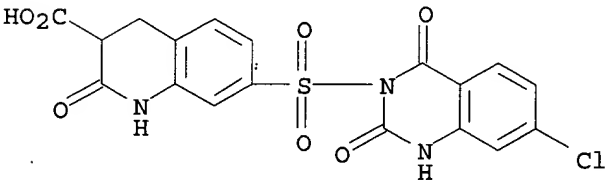
RN 259536-83-9 CAPLUS
CN Benzoic acid, 2-amino-5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



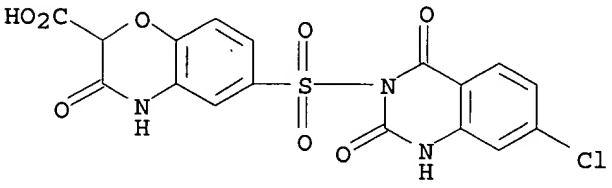
RN 259536-84-0 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-methoxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



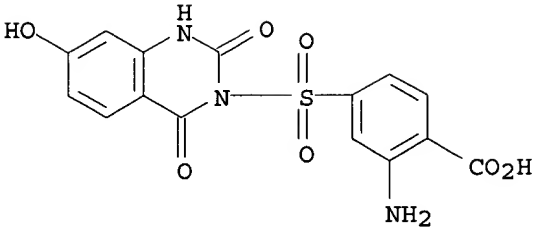
RN 259536-85-1 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1,2,3,4-tetrahydro-2-oxo- (9CI) (CA INDEX NAME)



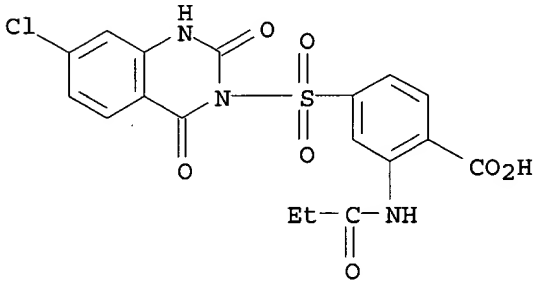
RN 259536-86-2 CAPLUS
CN 2H-1,4-Benzoxazine-2-carboxylic acid, 6-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-3,4-dihydro-3-oxo- (9CI) (CA INDEX NAME)



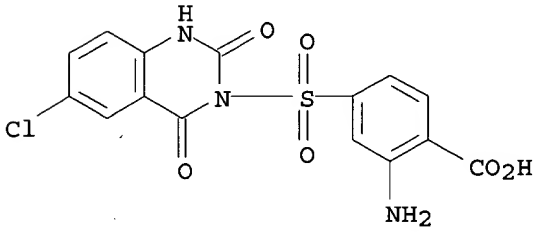
RN 259536-87-3 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-hydroxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



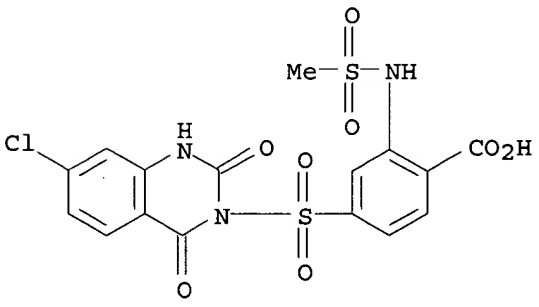
RN 259536-88-4 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(1-oxopropyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-89-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



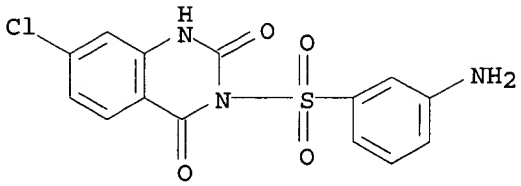
RN 259536-90-8 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-91-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro-, monomethanesulfonate (9CI) (CA INDEX NAME)

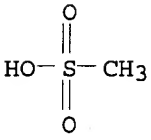
CM 1

CRN 259536-69-1
CMF C14 H10 Cl N3 O4 S

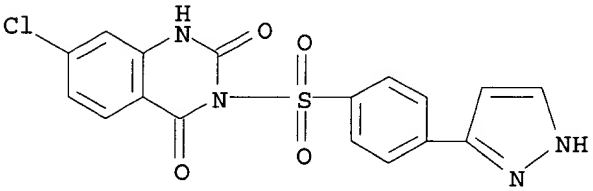


CM 2

CRN 75-75-2
CMF C H4 O3 S

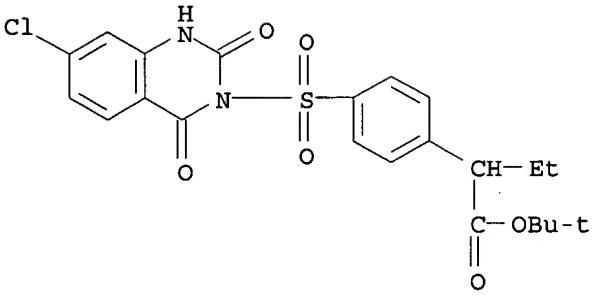


RN 357423-99-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

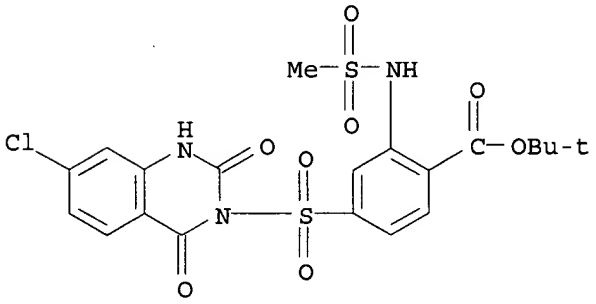


● HCl

IT **259536-95-3P 259537-12-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preventive or therapeutic drugs for dermatitises contg. chymase inhibitors as the active ingredient)
RN 259536-95-3 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 259537-12-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:635929 CAPLUS
DOCUMENT NUMBER: 135:205577
TITLE: Preventive or therapeutic drugs for various eosinophilia-related diseases containing chymase inhibitors as the active ingredient
INVENTOR(S): Fukami, Harukazu; Watanabe, Naohiro
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062293	A1	20010830	WO 2001-JP1322	20010222
W: AU, CA, CN, HU, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1174151	A1	20020123	EP 2001-906225	20010222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

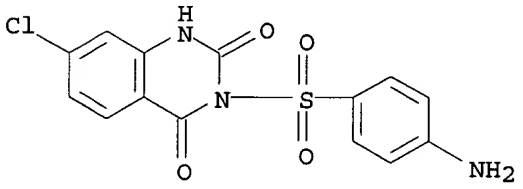
PRIORITY APPLN. INFO.: JP 2000-50487 A 20000222
WO 2001-JP1322 W 20010222

AB Preventive or therapeutic drugs, which inhibit the progression of

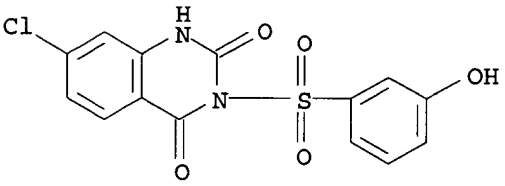
eosinophilia-related diseases while preventing the progression of various complications, and are so safe by virtue of their being free from adverse effects as to bring about enhancement in the quality of daily life of a patient. Specifically, preventive or therapeutic drugs for eosinophilia-related diseases contg. chymase inhibitors as the active ingredient, wherein the chymase inhibitors are quinazoline derivs. of the general formula (I) or pharmacol. acceptable salts thereof: (I).

IT **189062-66-6P 259536-59-9P 259536-60-2P**
259536-61-3P 259536-62-4P 259536-63-5P
259536-64-6P 259536-65-7P 259536-66-8P
259536-67-9P 259536-68-0P 259536-69-1P
259536-70-4P 259536-71-5P 259536-72-6P
259536-73-7P 259536-74-8P 259536-75-9P
259536-76-0P 259536-77-1P 259536-78-2P
259536-79-3P 259536-80-6P 259536-81-7P
259536-82-8P 259536-83-9P 259536-84-0P
259536-85-1P 259536-86-2P 259536-87-3P
259536-88-4P 259536-89-5P 259536-90-8P
259536-91-9P 357423-99-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preventive or therapeutic drugs for various eosinophilia-related diseases contg. chymase inhibitors as the active ingredient)

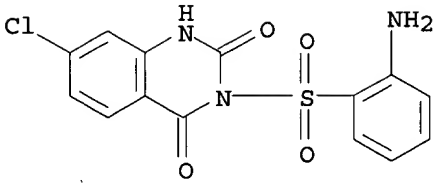
RN 189062-66-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



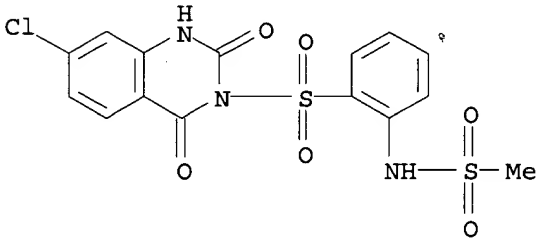
RN 259536-59-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



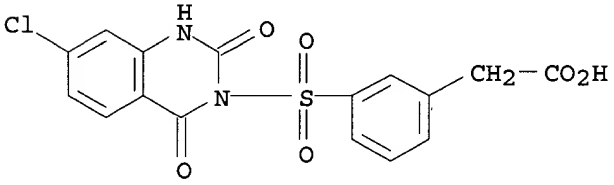
RN 259536-60-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(2-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



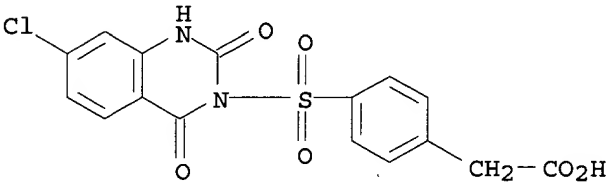
RN 259536-61-3 CAPLUS
CN Methanesulfonamide, N-[2-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



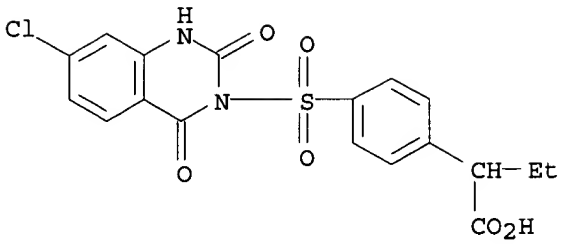
RN 259536-62-4 CAPLUS
CN Benzeneacetic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



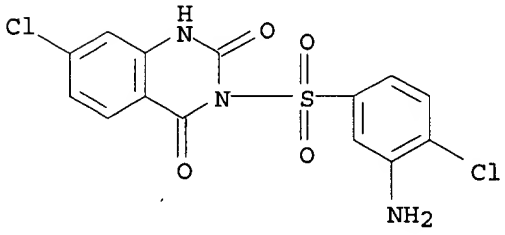
RN 259536-63-5 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



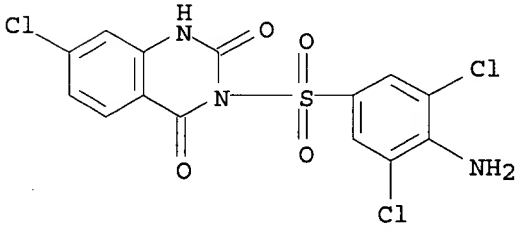
RN 259536-64-6 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl- (9CI) (CA INDEX NAME)



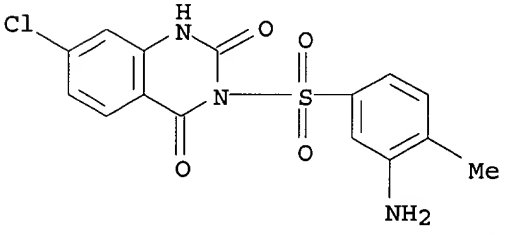
RN 259536-65-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-chlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



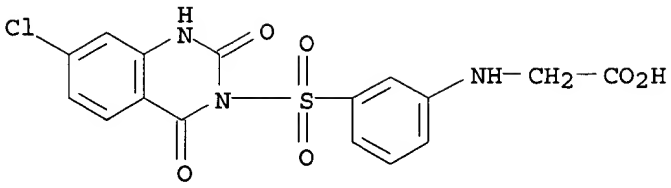
RN 259536-66-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-amino-3,5-dichlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



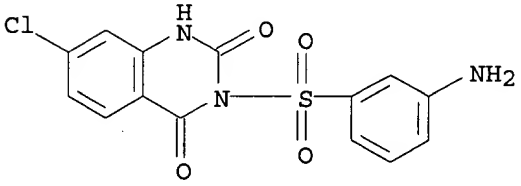
RN 259536-67-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



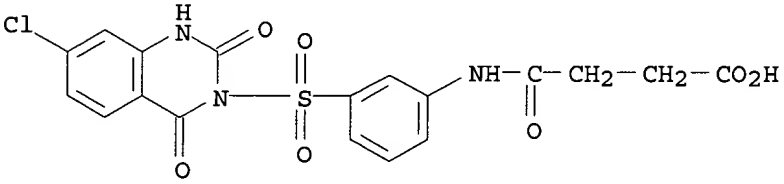
RN 259536-68-0 CAPLUS
CN Glycine, N-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



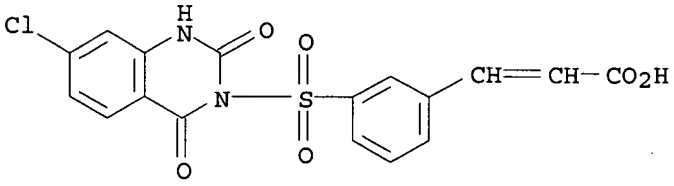
RN 259536-69-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



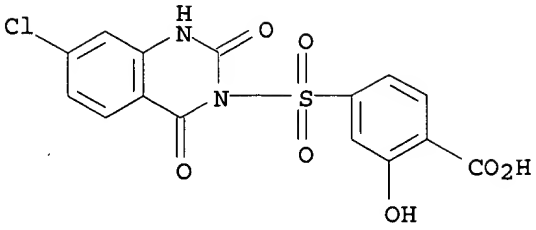
RN 259536-70-4 CAPLUS
CN Butanoic acid, 4-[[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]amino]-4-oxo- (9CI) (CA INDEX NAME)



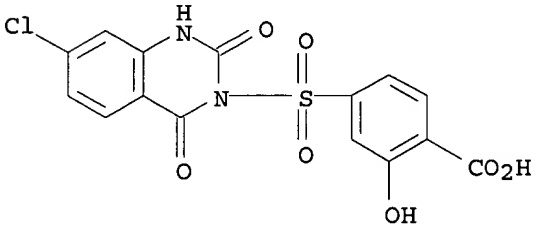
RN 259536-71-5 CAPLUS
CN 2-Propenoic acid, 3-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 259536-72-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)

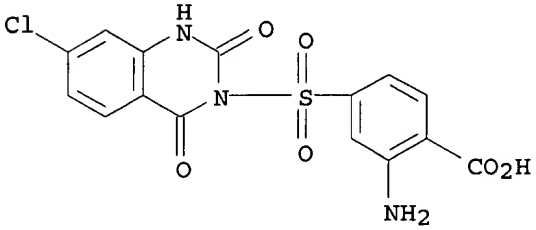


RN 259536-73-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy-, monosodium salt (9CI) (CA INDEX NAME)

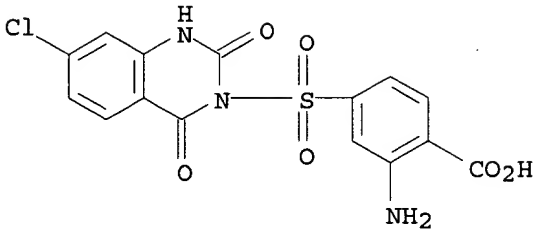


● Na

RN 259536-74-8 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)

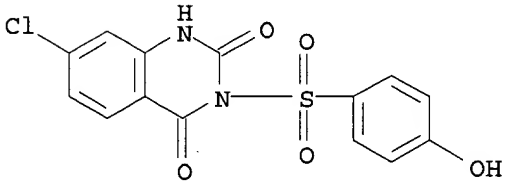


RN 259536-75-9 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)

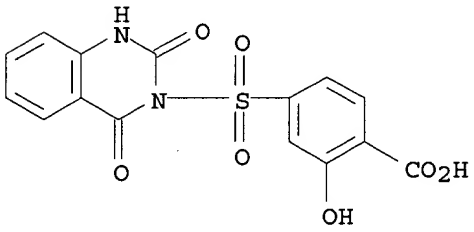


● Na

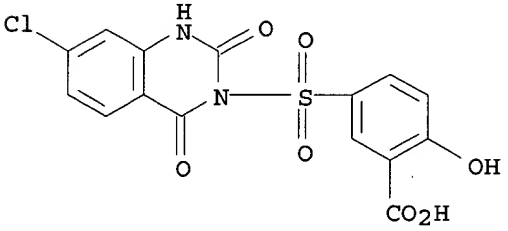
RN 259536-76-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



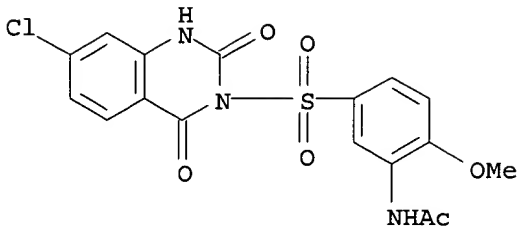
RN 259536-77-1 CAPLUS
CN Benzoic acid, 4-[(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



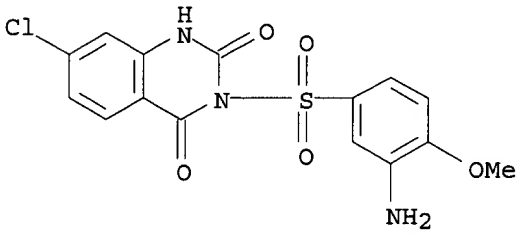
RN 259536-78-2 CAPLUS
CN Benzoic acid, 5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



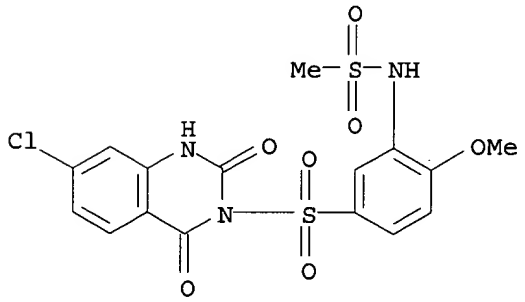
RN 259536-79-3 CAPLUS
CN Acetamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



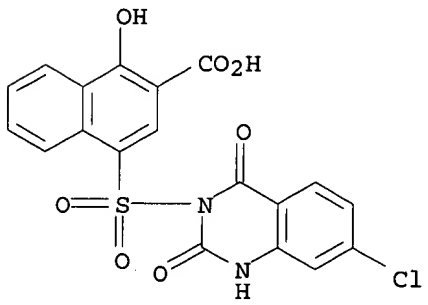
RN 259536-80-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methoxyphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



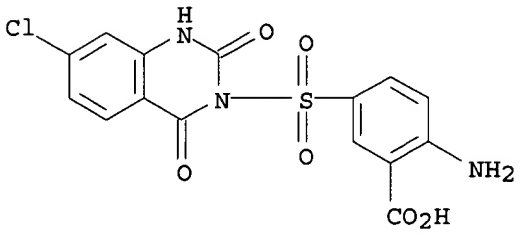
RN 259536-81-7 CAPLUS
CN Methanesulfonamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



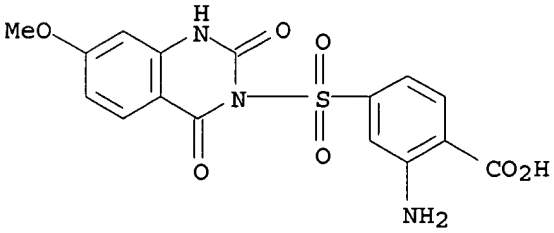
RN 259536-82-8 CAPLUS
CN 2-Naphthalenecarboxylic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1-hydroxy- (9CI) (CA INDEX NAME)



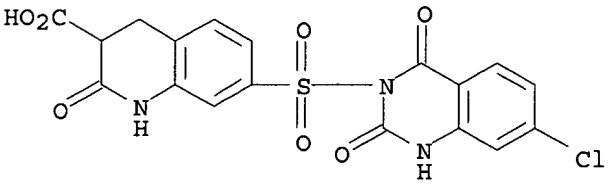
RN 259536-83-9 CAPLUS
CN Benzoic acid, 2-amino-5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



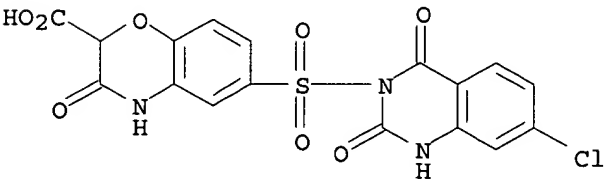
RN 259536-84-0 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-methoxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



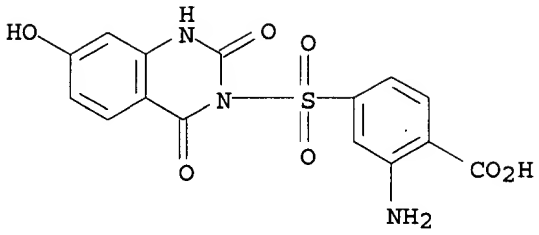
RN 259536-85-1 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1,2,3,4-tetrahydro-2-oxo- (9CI) (CA INDEX NAME)



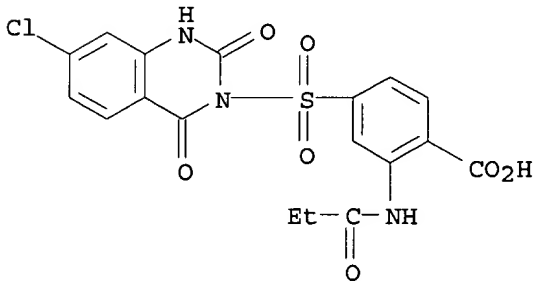
RN 259536-86-2 CAPLUS
CN 2H-1,4-Benzoxazine-2-carboxylic acid, 6-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-3,4-dihydro-3-oxo- (9CI) (CA INDEX NAME)



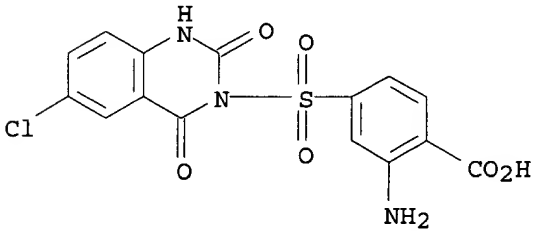
RN 259536-87-3 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-hydroxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



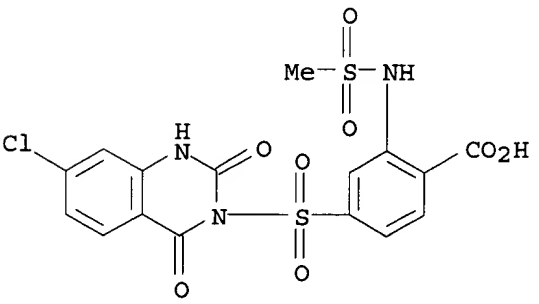
RN 259536-88-4 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(1-oxopropyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-89-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



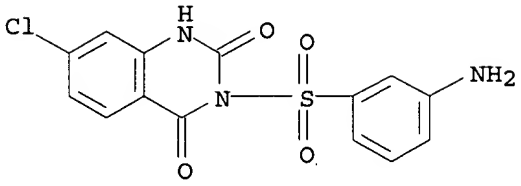
RN 259536-90-8 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-91-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro-, monomethanesulfonate (9CI) (CA INDEX NAME)

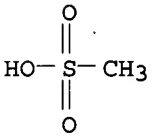
CM 1

CRN 259536-69-1
CMF C14 H10 Cl N3 O4 S

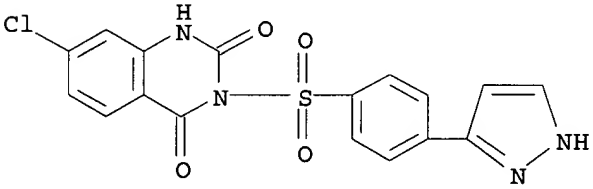


CM 2

CRN 75-75-2
CMF C H4 O3 S

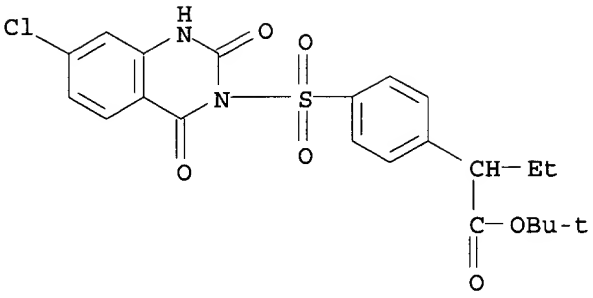


RN 357423-99-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

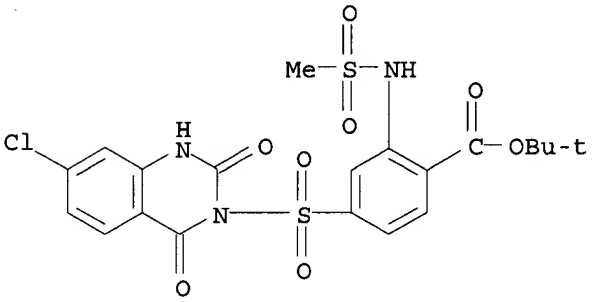


● HCl

IT **259536-95-3P 259537-12-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preventive or therapeutic drugs for various eosinophilia-related diseases contg. chymase inhibitors as the active ingredient)
RN 259536-95-3 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 259537-12-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:635928 CAPLUS
DOCUMENT NUMBER: 135:205560
TITLE: Preventive or therapeutic drugs for fibrosis containing chymase inhibitors as the active ingredient
INVENTOR(S): Fukami, Harukazu; Okunishi, Hideki; Kakizoe, Eiichi
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062292	A1	20010830	WO 2001-JP1321	20010222
W: AU, CA, CN, HU, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1192949	A1	20020403	EP 2001-906224	20010222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

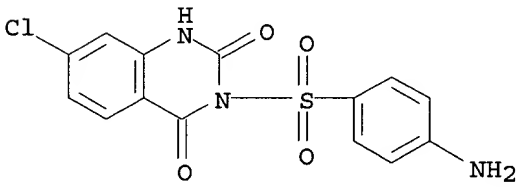
PRIORITY APPLN. INFO.: JP 2000-50502 A 20000222
WO 2001-JP1321 W 20010222

AB Preventive or therapeutic drugs, which inhibit the progression of fibrogenesis in the skin or other various organs while preventing the

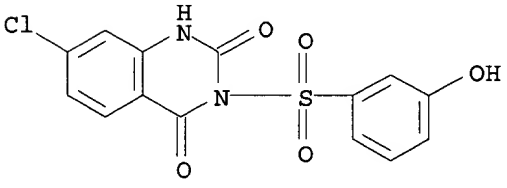
progression of various complications, and are so safe by virtue of their being free from adverse effects as to bring about enhancement in the quality of daily life of a patient. Specifically, preventive or therapeutic drugs for fibrosis contg. chymase inhibitors as the active ingredient, wherein the chymase inhibitors are quinazoline derivs. of the general formula (I) or pharmacol. acceptable salts thereof.

IT **189062-66-6P 259536-59-9P 259536-60-2P**
259536-61-3P 259536-62-4P 259536-63-5P
259536-64-6P 259536-65-7P 259536-66-8P
259536-67-9P 259536-68-0P 259536-69-1P
259536-70-4P 259536-71-5P 259536-72-6P
259536-73-7P 259536-74-8P 259536-75-9P
259536-76-0P 259536-77-1P 259536-78-2P
259536-79-3P 259536-80-6P 259536-81-7P
259536-82-8P 259536-83-9P 259536-84-0P
259536-85-1P 259536-86-2P 259536-87-3P
259536-88-4P 259536-89-5P 259536-90-8P
259536-91-9P 357423-99-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preventive or therapeutic drugs for fibrosis contg. chymase inhibitors as the active ingredient)

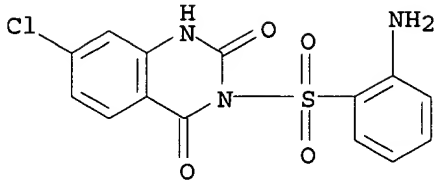
RN 189062-66-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



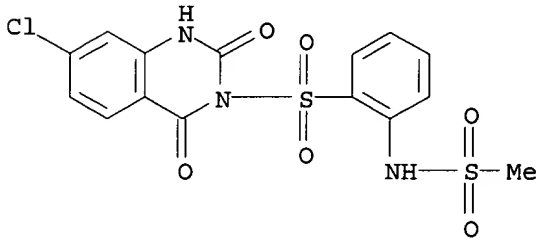
RN 259536-59-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



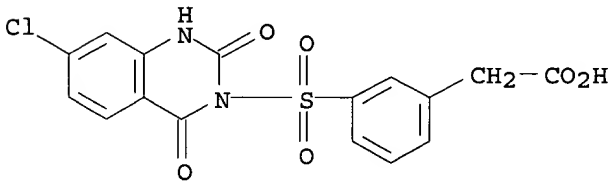
RN 259536-60-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(2-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



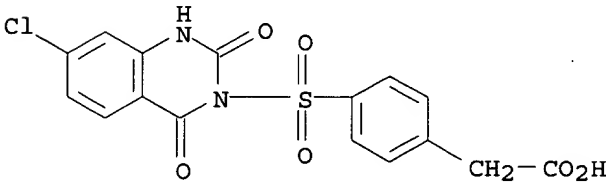
RN 259536-61-3 CAPLUS
CN Methanesulfonamide, N-[2-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



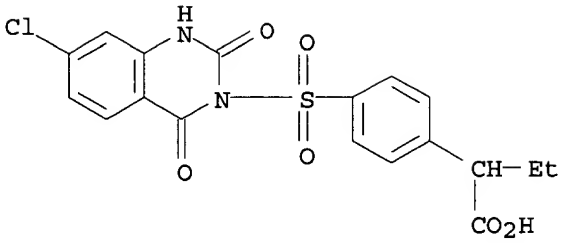
RN 259536-62-4 CAPLUS
CN Benzeneacetic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



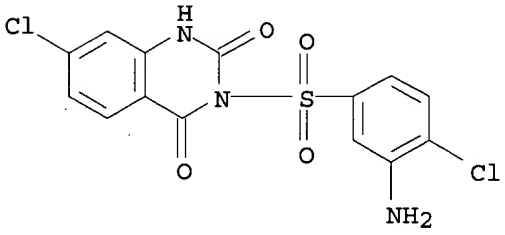
RN 259536-63-5 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



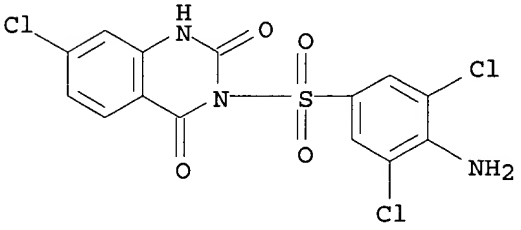
RN 259536-64-6 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl- (9CI) (CA INDEX NAME)



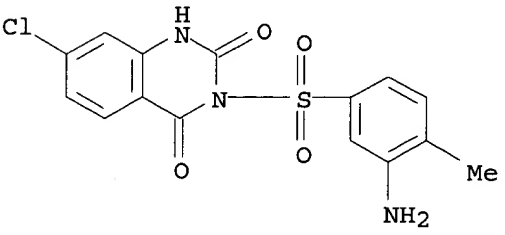
RN 259536-65-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-chlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



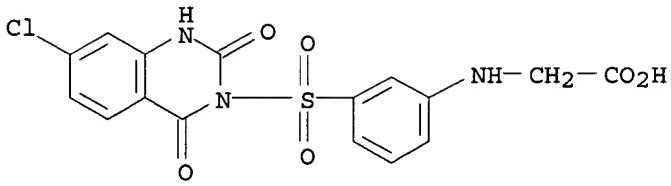
RN 259536-66-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-amino-3,5-dichlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



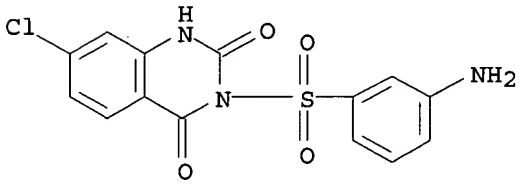
RN 259536-67-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



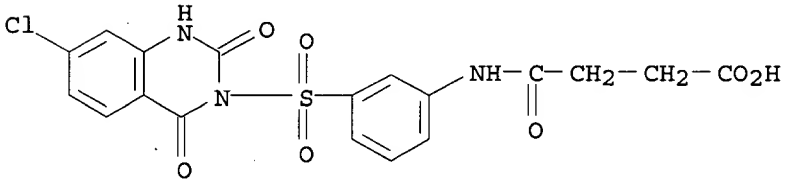
RN 259536-68-0 CAPLUS
CN Glycine, N-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



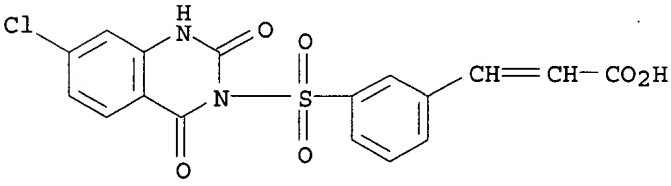
RN 259536-69-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



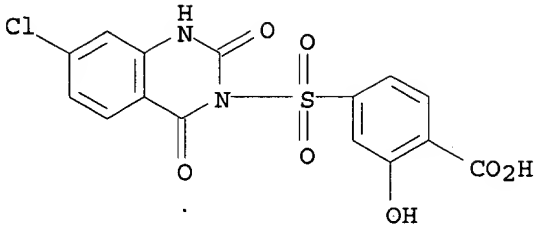
RN 259536-70-4 CAPLUS
CN Butanoic acid, 4-[[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]amino]-4-oxo- (9CI) (CA INDEX NAME)



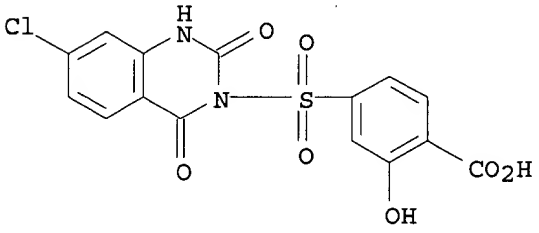
RN 259536-71-5 CAPLUS
CN 2-Propenoic acid, 3-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 259536-72-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)

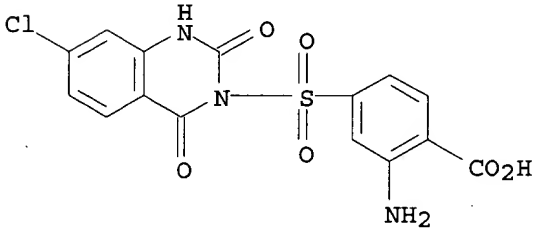


RN 259536-73-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy-, monosodium salt (9CI) (CA INDEX NAME)

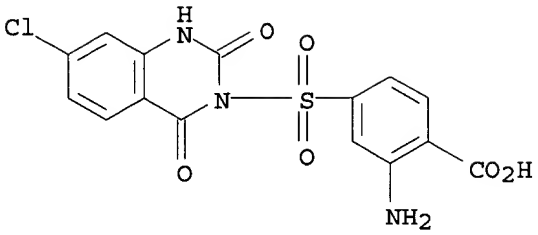


● Na

RN 259536-74-8 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)

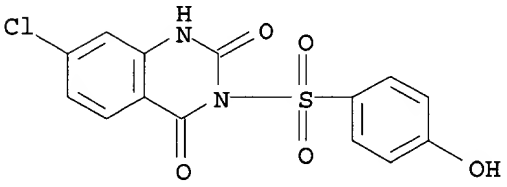


RN 259536-75-9 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)

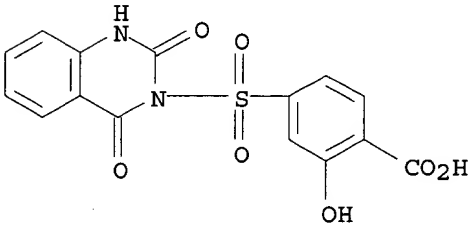


● Na

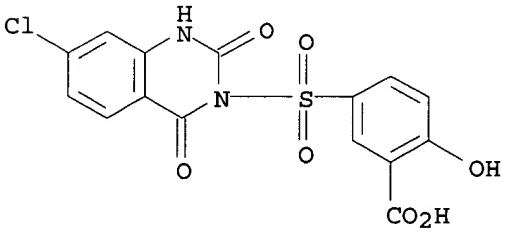
RN 259536-76-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



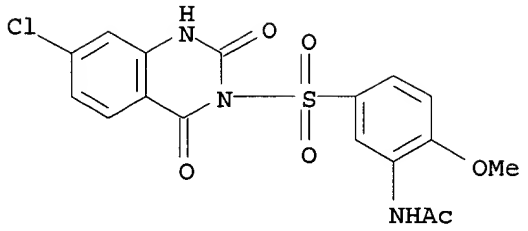
RN 259536-77-1 CAPLUS
CN Benzoic acid, 4-[(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



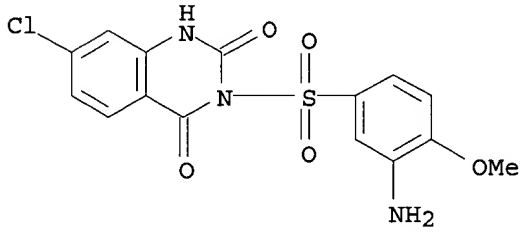
RN 259536-78-2 CAPLUS
CN Benzoic acid, 5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



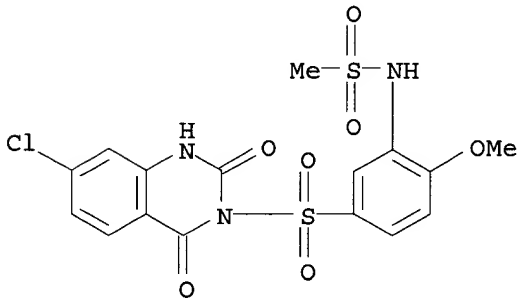
RN 259536-79-3 CAPLUS
CN Acetamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



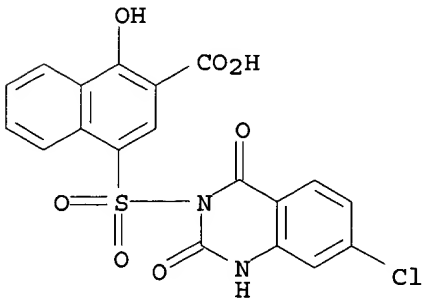
RN 259536-80-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methoxyphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



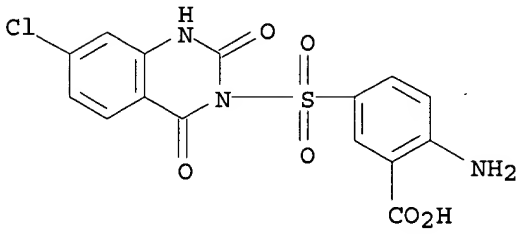
RN 259536-81-7 CAPLUS
CN Methanesulfonamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



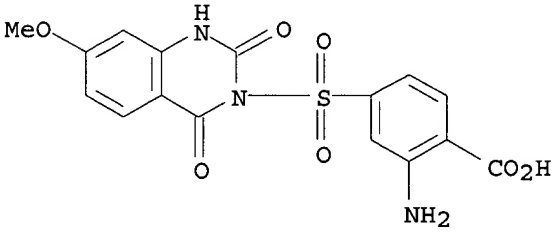
RN 259536-82-8 CAPLUS
CN 2-Naphthalenecarboxylic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1-hydroxy- (9CI) (CA INDEX NAME)



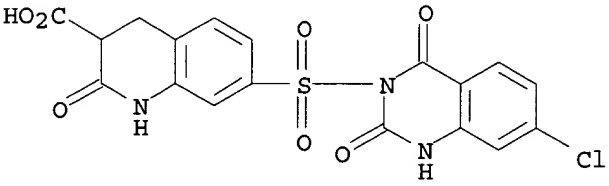
RN 259536-83-9 CAPLUS
CN Benzoic acid, 2-amino-5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



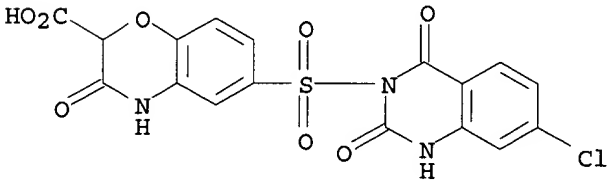
RN 259536-84-0 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-methoxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



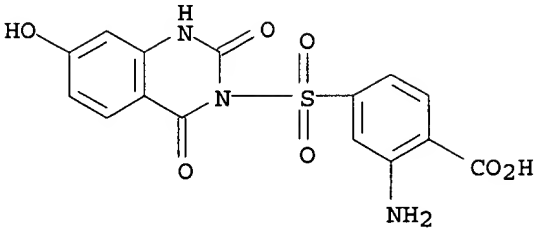
RN 259536-85-1 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1,2,3,4-tetrahydro-2-oxo- (9CI) (CA INDEX NAME)



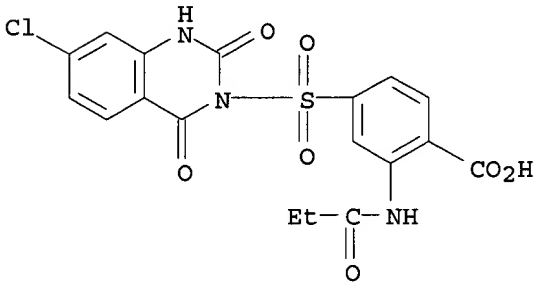
RN 259536-86-2 CAPLUS
CN 2H-1,4-Benzoxazine-2-carboxylic acid, 6-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-3,4-dihydro-3-oxo- (9CI) (CA INDEX NAME)



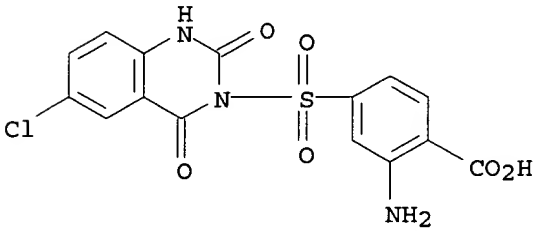
RN 259536-87-3 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-hydroxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



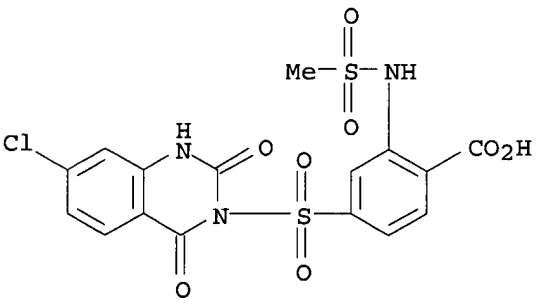
RN 259536-88-4 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(1-oxopropyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-89-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



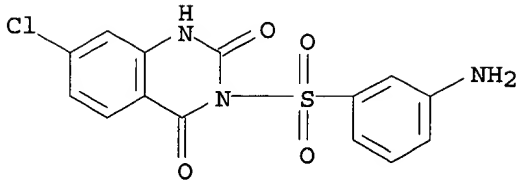
RN 259536-90-8 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-91-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro-, monomethanesulfonate (9CI) (CA INDEX NAME)

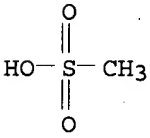
CM 1

CRN 259536-69-1
CMF C14 H10 Cl N3 O4 S

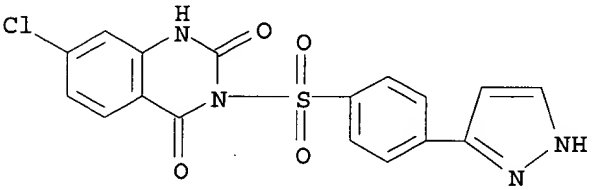


CM 2

CRN 75-75-2
CMF C H4 O3 S

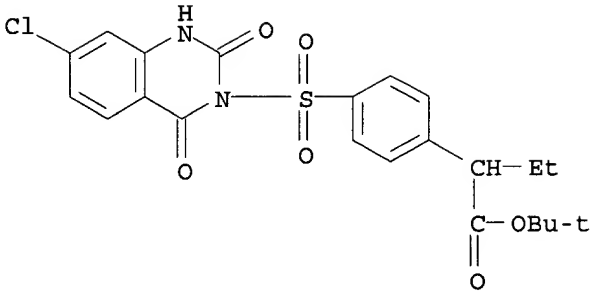


RN 357423-99-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

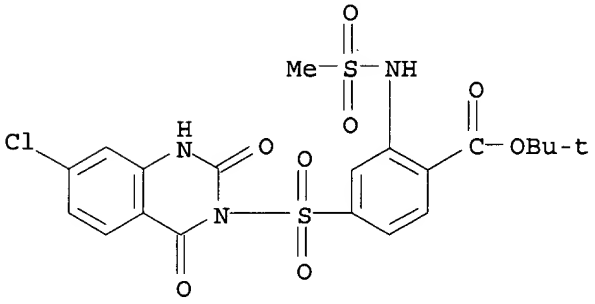


● HCl

IT **259536-95-3P 259537-12-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preventive or therapeutic drugs for fibrosis contg. chymase inhibitors as the active ingredient)
RN 259536-95-3 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 259537-12-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

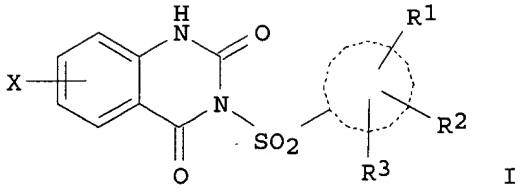
L11 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338384 CAPLUS
DOCUMENT NUMBER: 134:348278
TITLE: Inhibitors against vascular lipid deposition containing chymase-inhibiting substances
INVENTOR(S): Fukami, Harukazu; Urata, Hidenori
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032214	A1	20010510	WO 2000-JP7706	20001101
W: AU, CA, CN, HU, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1142586	A1	20011010	EP 2000-971729	20001101
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1999-311257 A 19991101
WO 2000-JP7706 W 20001101

GI

S. I. C. Applicant's own PCT



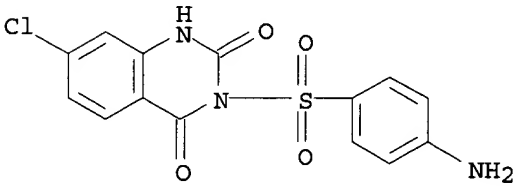
I

AB Preventive or therapeutic agents for diseases accompanied with vascular function disorders related to deposition of lipid on vessel walls, contg. specific chymase inhibitors as the active ingredient. Quinazoline derivs. of general formula (I) are usable as the specific chymase inhibitor. In said formula, A is an arom. ring.

IT **189062-66-6P 259536-59-9P 259536-60-2P**
259536-61-3P 259536-62-4P 259536-63-5P
259536-64-6P 259536-65-7P 259536-66-8P
259536-67-9P 259536-68-0P 259536-69-1P
259536-70-4P 259536-71-5P 259536-72-6P
259536-73-7P 259536-74-8P 259536-75-9P
259536-76-0P 259536-77-1P 259536-78-2P
259536-79-3P 259536-80-6P 259536-81-7P
259536-82-8P 259536-83-9P 259536-84-0P
259536-85-1P 259536-86-2P 259536-87-3P
259536-88-4P 259536-89-5P 259536-91-9P
338998-94-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors against vascular lipid deposition contg. quinazoline chymase-inhibiting substances)

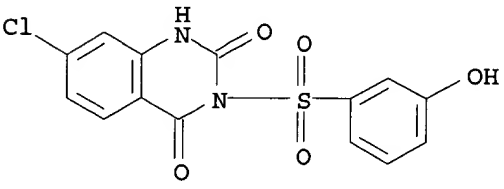
RN 189062-66-6 CAPLUS

CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



RN 259536-59-9 CAPLUS

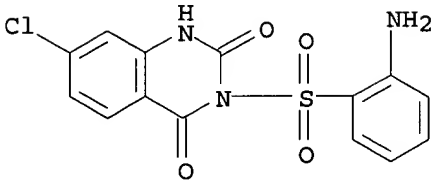
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



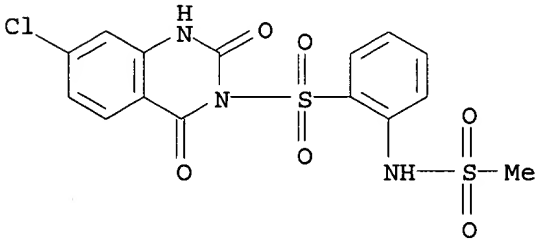
RN 259536-60-2 CAPLUS

CN 2,4(1H,3H)-Quinazolinedione, 3-[(2-aminophenyl)sulfonyl]-7-chloro- (9CI)

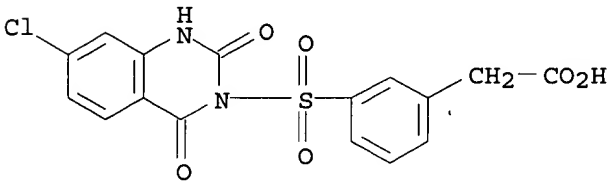
(CA INDEX NAME)



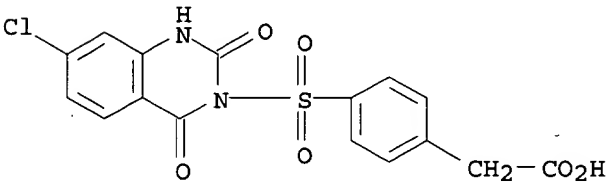
RN 259536-61-3 CAPLUS
CN Methanesulfonamide, N-[2-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



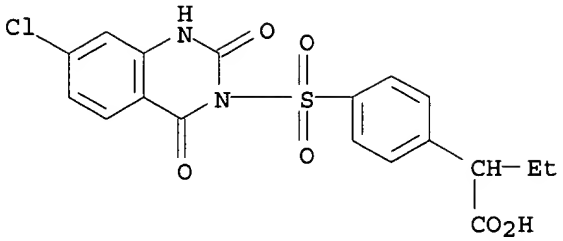
RN 259536-62-4 CAPLUS
CN Benzeneacetic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



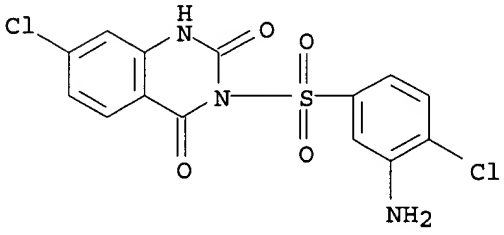
RN 259536-63-5 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



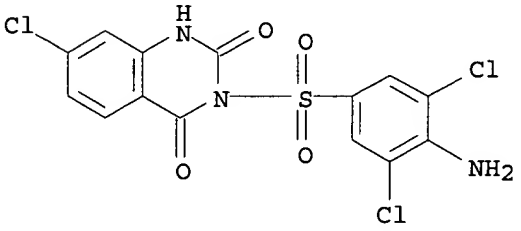
RN 259536-64-6 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl- (9CI) (CA INDEX NAME)



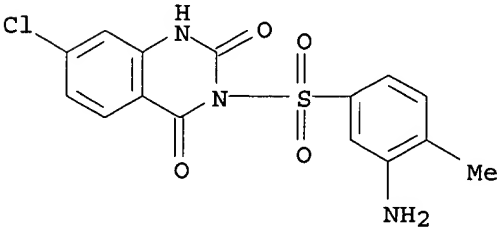
RN 259536-65-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-chlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



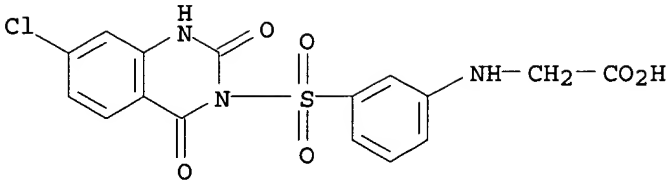
RN 259536-66-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-amino-3,5-dichlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



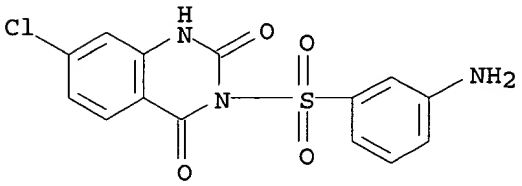
RN 259536-67-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



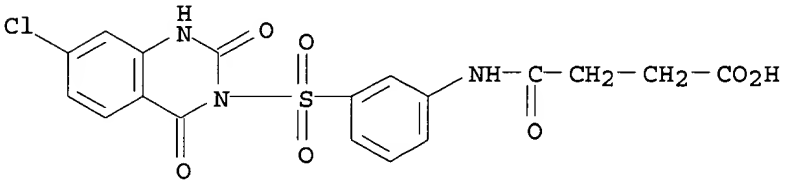
RN 259536-68-0 CAPLUS
CN Glycine, N-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



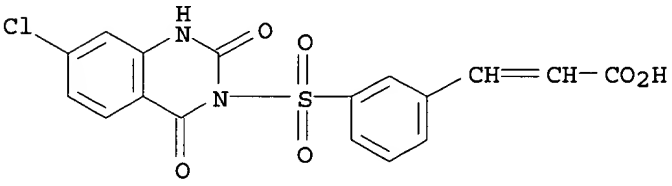
RN 259536-69-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



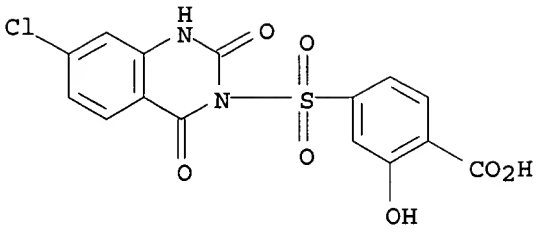
RN 259536-70-4 CAPLUS
CN Butanoic acid, 4-[[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]amino]-4-oxo- (9CI) (CA INDEX NAME)



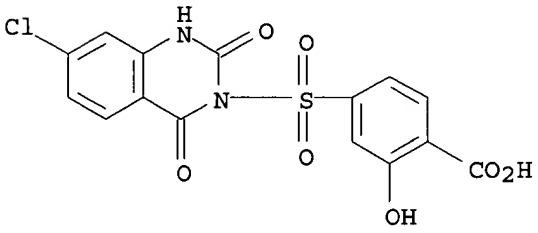
RN 259536-71-5 CAPLUS
CN 2-Propenoic acid, 3-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 259536-72-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)

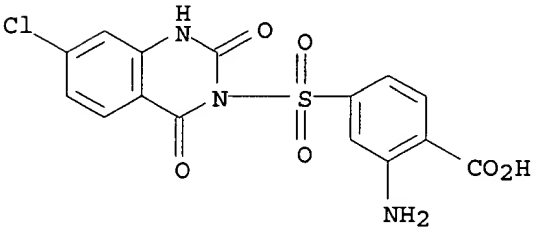


RN 259536-73-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy-, monosodium salt (9CI) (CA INDEX NAME)

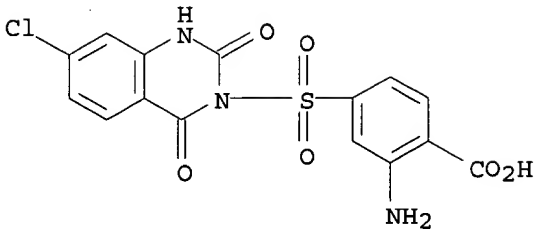


● Na

RN 259536-74-8 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)

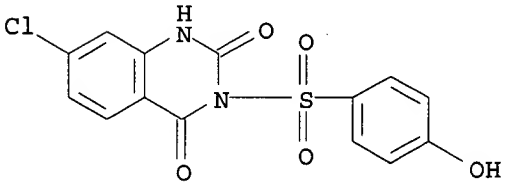


RN 259536-75-9 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)

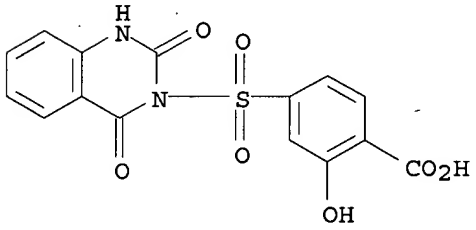


● Na

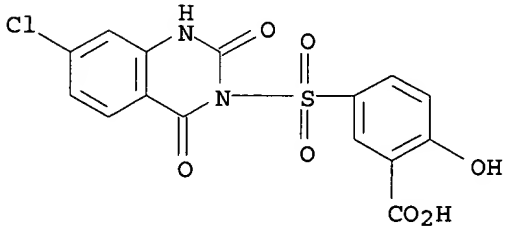
RN 259536-76-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



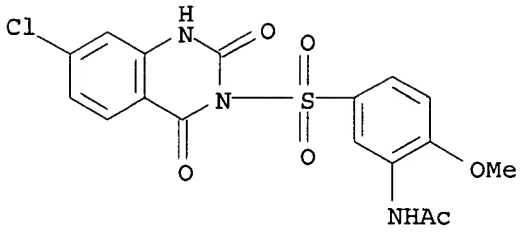
RN 259536-77-1 CAPLUS
CN Benzoic acid, 4-[(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



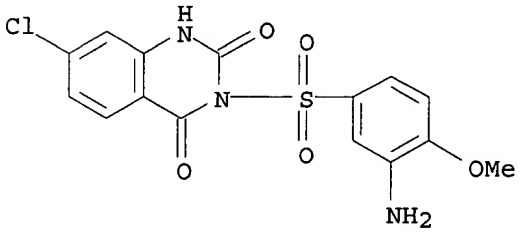
RN 259536-78-2 CAPLUS
CN Benzoic acid, 5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



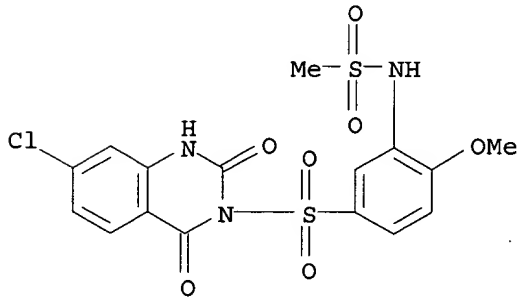
RN 259536-79-3 CAPLUS
CN Acetamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



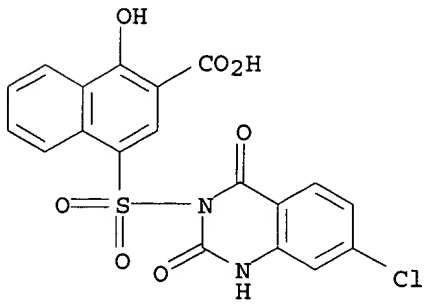
RN 259536-80-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methoxyphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



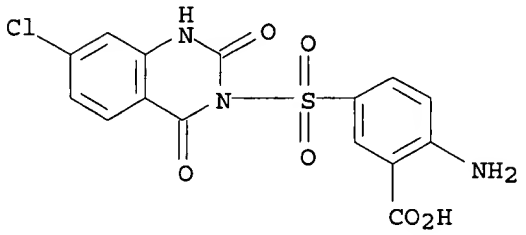
RN 259536-81-7 CAPLUS
CN Methanesulfonamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



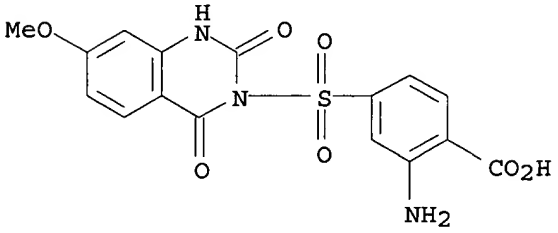
RN 259536-82-8 CAPLUS
CN 2-Naphthalenecarboxylic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1-hydroxy- (9CI) (CA INDEX NAME)



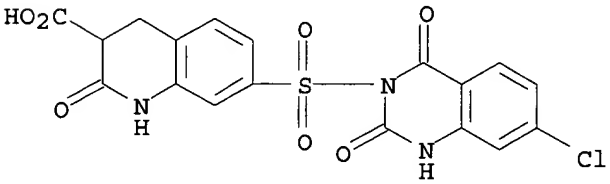
RN 259536-83-9 CAPLUS
CN Benzoic acid, 2-amino-5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



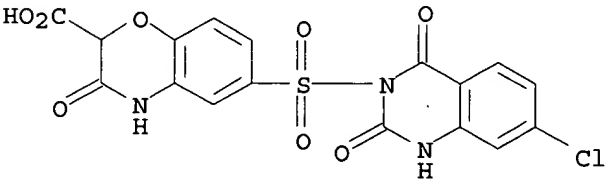
RN 259536-84-0 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-methoxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



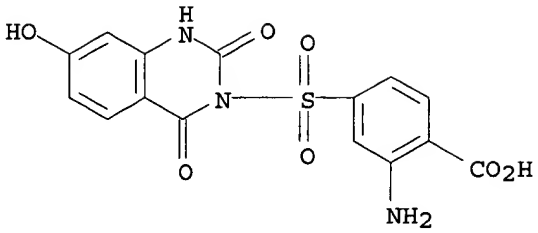
RN 259536-85-1 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1,2,3,4-tetrahydro-2-oxo- (9CI) (CA INDEX NAME)



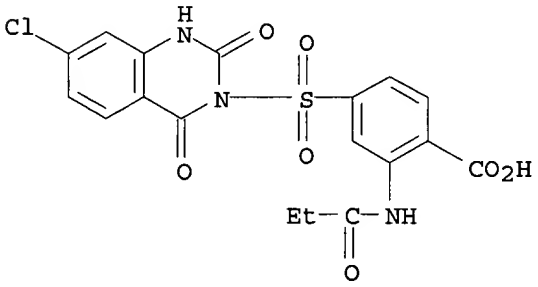
RN 259536-86-2 CAPLUS
CN 2H-1,4-Benzoxazine-2-carboxylic acid, 6-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-3,4-dihydro-3-oxo- (9CI) (CA INDEX NAME)



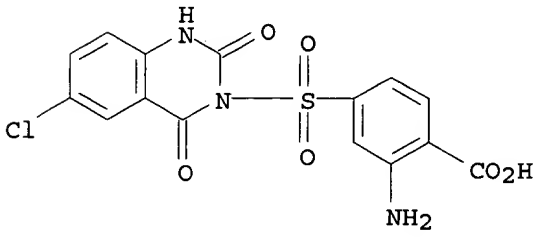
RN 259536-87-3 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-hydroxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 259536-88-4 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(1-oxopropyl)amino]- (9CI) (CA INDEX NAME)



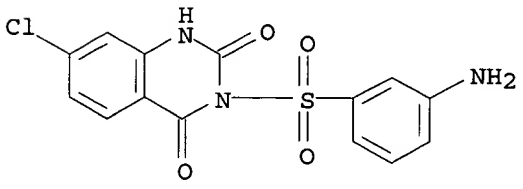
RN 259536-89-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 259536-91-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro-, monomethanesulfonate (9CI) (CA INDEX NAME)

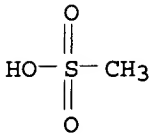
CM 1

CRN 259536-69-1
CMF C14 H10 Cl N3 O4 S

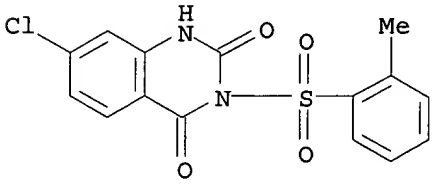


CM 2

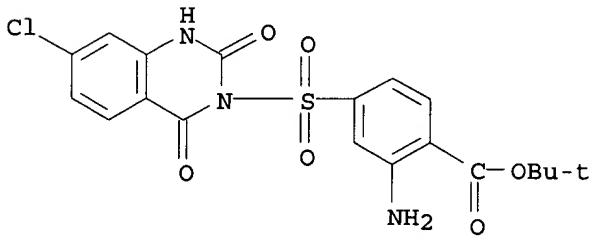
CRN 75-75-2
CMF C H4 O3 S



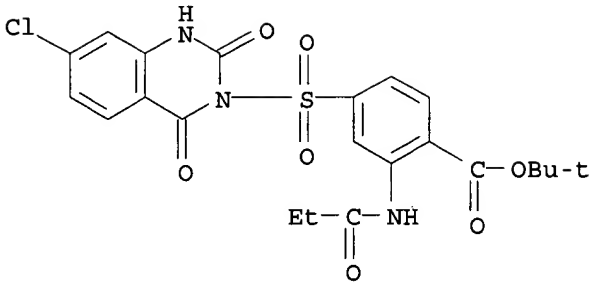
RN 338998-94-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



IT **259537-02-5P 338998-96-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors against vascular lipid deposition contg. quinazoline chymase-inhibiting substances)
RN 259537-02-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 338998-96-2 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(1-oxopropyl)amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



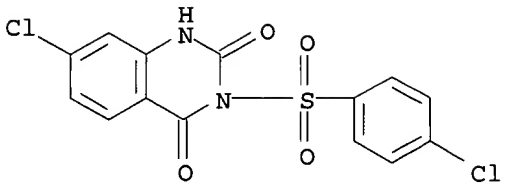
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:530563 CAPLUS
DOCUMENT NUMBER: 133:248824
TITLE: Substituted 3-phenylsulfonylquinazoline-2,4-dione derivatives as novel nonpeptide inhibitors of human heart chymase
AUTHOR(S): Fukami, Harukazu; Imajo, Seiichi; Ito, Akiko; Kakutani, Saki; Shibata, Hiroshi; Sumida, Motoo; Tanaka, Taisaku; Niwata, Shinjiro; Saitoh, Masayuki; Kiso, Yoshinobu; Miyazaki, Mizuo; Okunishi, Hideki; Urata, Hidenori; Arakawa, Kikuo
CORPORATE SOURCE: Institute for Biomedical Research, Suntory Ltd., Osaka, 618-8503, Japan
SOURCE: Drug Design and Discovery (2000), 17(1), 69-84
CODEN: DDDIEV; ISSN: 1055-9612
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

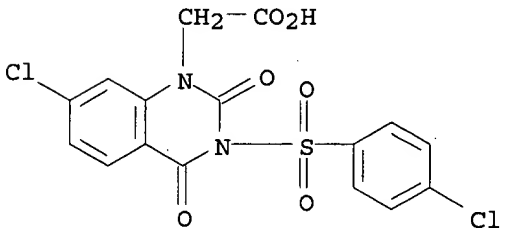
AB A series of 3-phenylsulfonylquinazoline-2,4-dione derivs. have been synthesized and evaluated for their ability to inhibit human heart chymase. The structure-activity relation studies on these compds. gave the following results. The Ph moiety of quinazoline participates in a hydrophobic interaction where an optimum size is required. In this moiety, 7-chloroquinazoline is the best moiety for inhibiting chymase, chymotrypsin and cathepsin G. A 3-phenylsulfonyl moiety substituted with hydrophobic electron-withdrawing groups at the 4-position potentiated the activity. Anthranil moiety also enhanced the activity. Pyridylmethyl and N-pyridylacetamide at the 1-position gave an IC50 in the order of 10-8M. Mol. modeling studies on the interaction of 7-chloro-3-(4-chlorophenylsulfonyl)quinazoline-2,4(1H, 3H)-dione with the active site of human heart chymase suggested that the Ph moiety of quinazoline interacts with the hydrophobic P1 pocket, the 3-phenylsulfonyl moiety resides in the S1'-S2' subsites, the moiety at the 1-position locates in the S2-S3 subsites and the 4-carbonyl and 3-sulfonyl group interact with the oxyanion hole and the His57 side-chain of chymase, resp.

IT **189061-05-0P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(substituted phenylsulfonylquinazolinedione derivs. as novel nonpeptide inhibitors of human heart chymase in relation to structure and inhibition of chymotrypsin and cathepsin G)

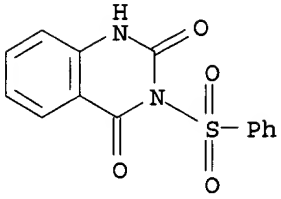
RN 189061-05-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



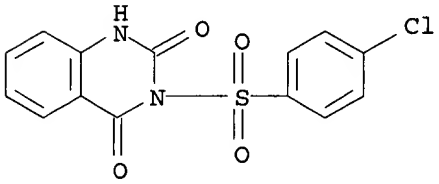
IT **189061-53-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(substituted phenylsulfonylquinazolinedione derivs. as novel nonpeptide inhibitors of human heart chymase in relation to structure and inhibition of chymotrypsin and cathepsin G)
RN 189061-53-8 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)



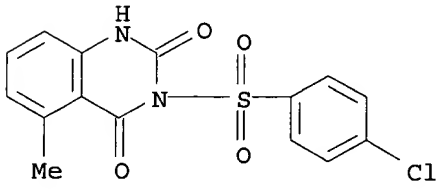
IT **116445-93-3P 116445-95-5P 189061-07-2P**
189061-10-7P 189061-12-9P 189061-16-3P
189061-18-5P 189061-20-9P 189061-22-1P
189061-24-3P 189061-26-5P 189061-29-8P
189061-31-2P 189061-35-6P 189061-37-8P
189061-43-6P 189061-45-8P 189061-46-9P
189061-47-0P 189061-48-1P 189061-51-6P
189061-54-9P 189061-56-1P 189061-59-4P
189061-60-7P 189061-75-4P 189061-76-5P
189061-77-6P 189061-81-2P 189062-34-8P
189062-35-9P 189062-36-0P 189062-46-2P
189062-47-3P 189062-51-9P 189062-52-0P
189062-55-3P 189062-61-1P 189062-66-6P
189062-67-7P 189062-69-9P 189062-70-2P
259536-59-9P 259536-69-1P 259536-72-6P
259536-74-8P 259536-76-0P 294865-37-5P
294865-38-6P 294865-39-7P 294865-40-0P
294865-41-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(substituted phenylsulfonylquinazolinedione derivs. as novel nonpeptide inhibitors of human heart chymase in relation to structure and inhibition of chymotrypsin and cathepsin G)
RN 116445-93-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



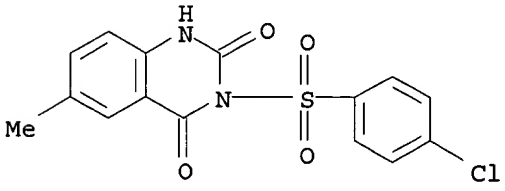
RN 116445-95-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



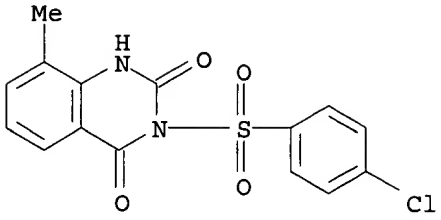
RN 189061-07-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-5-methyl- (9CI) (CA INDEX NAME)



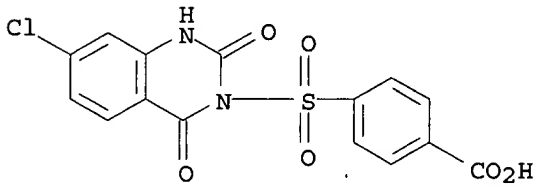
RN 189061-10-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6-methyl- (9CI) (CA INDEX NAME)



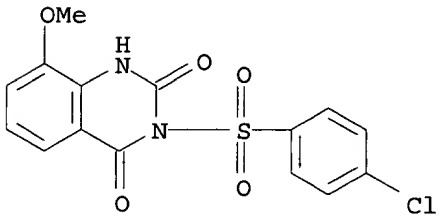
RN 189061-12-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-8-methyl- (9CI) (CA INDEX NAME)



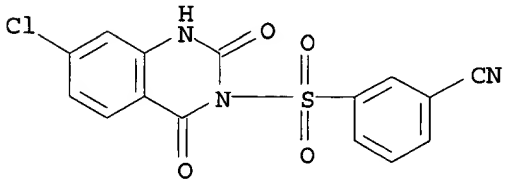
RN 189061-16-3 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



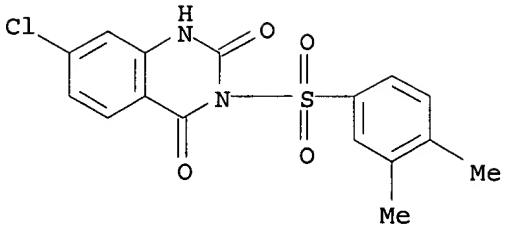
RN 189061-18-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-8-methoxy- (9CI) (CA INDEX NAME)



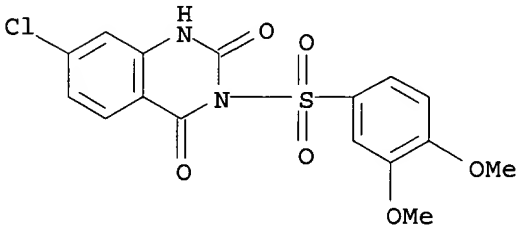
RN 189061-20-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-cyanophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



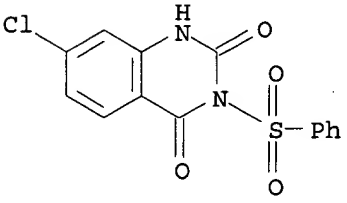
RN 189061-22-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3,4-dimethylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



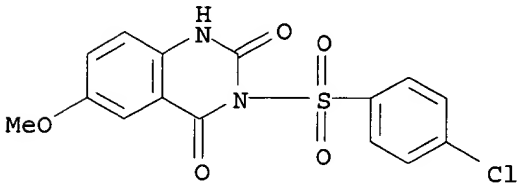
RN 189061-24-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3,4-dimethoxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



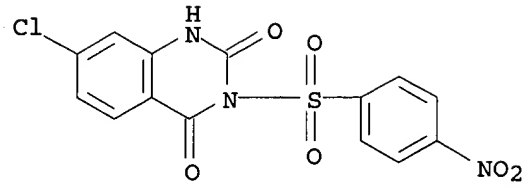
RN 189061-26-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



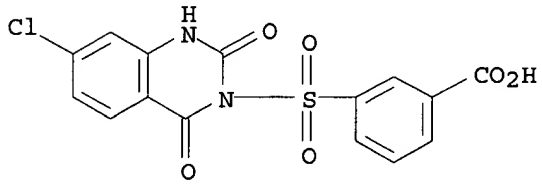
RN 189061-29-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6-methoxy- (9CI) (CA INDEX NAME)



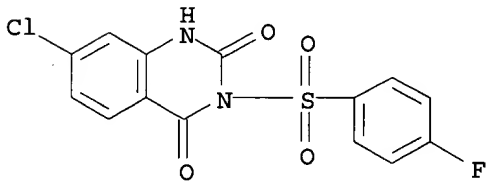
RN 189061-31-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-nitrophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



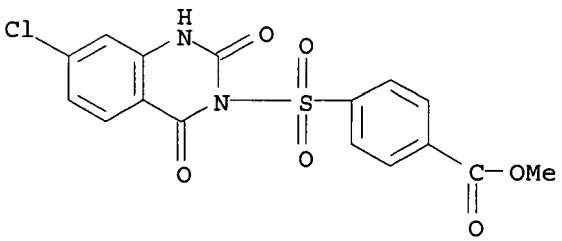
RN 189061-35-6 CAPLUS
CN Benzoic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



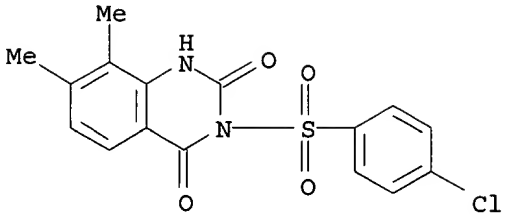
RN 189061-37-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-fluorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



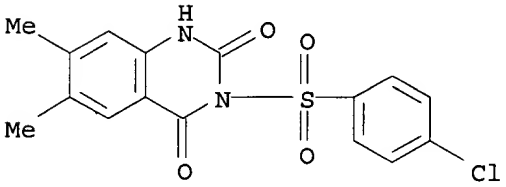
RN 189061-43-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)



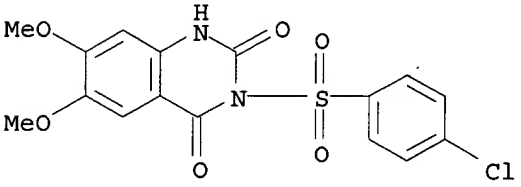
RN 189061-45-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7,8-dimethyl- (9CI) (CA INDEX NAME)



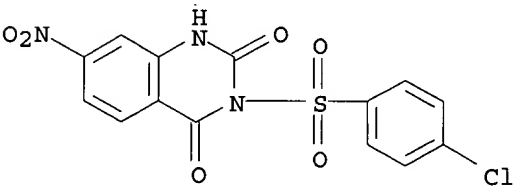
RN 189061-46-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6,7-dimethyl- (9CI) (CA INDEX NAME)



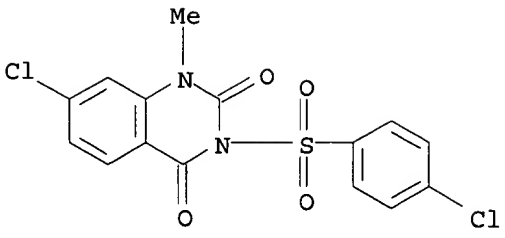
RN 189061-47-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6,7-dimethoxy- (9CI) (CA INDEX NAME)



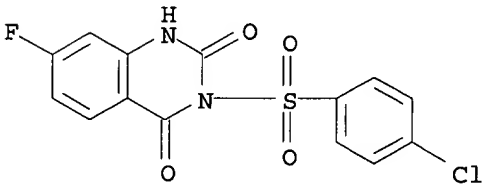
RN 189061-48-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-nitro- (9CI) (CA INDEX NAME)



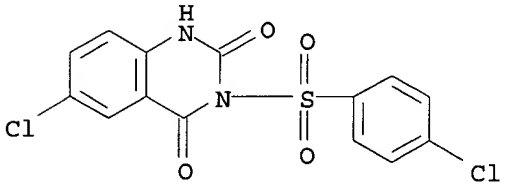
RN 189061-51-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-methyl- (9CI) (CA INDEX NAME)



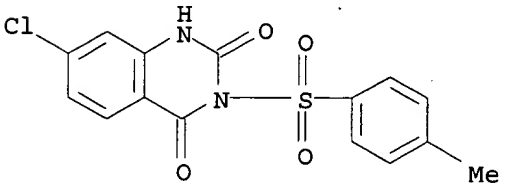
RN 189061-54-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-fluoro- (9CI) (CA INDEX NAME)



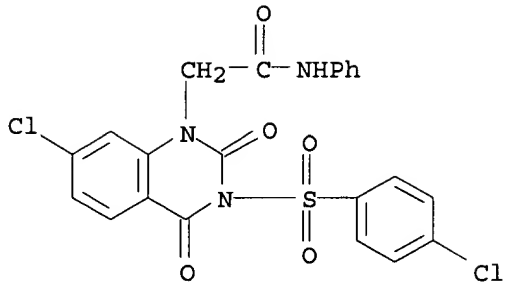
RN 189061-56-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 6-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



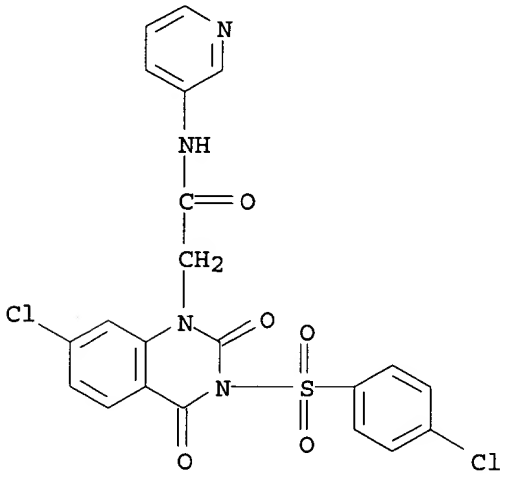
RN 189061-59-4 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



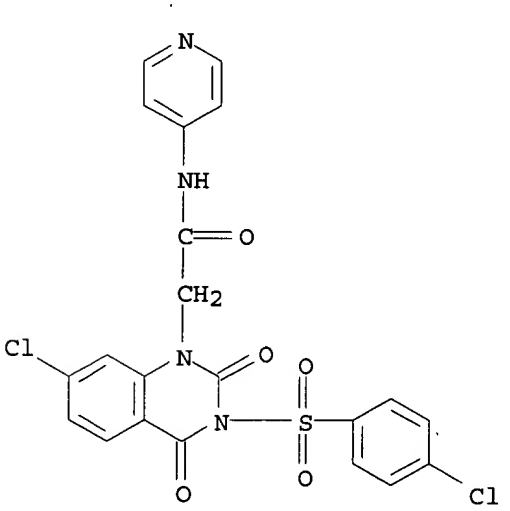
RN 189061-60-7 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-phenyl- (9CI) (CA INDEX NAME)



RN 189061-75-4 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-3-pyridinyl- (9CI) (CA INDEX NAME)

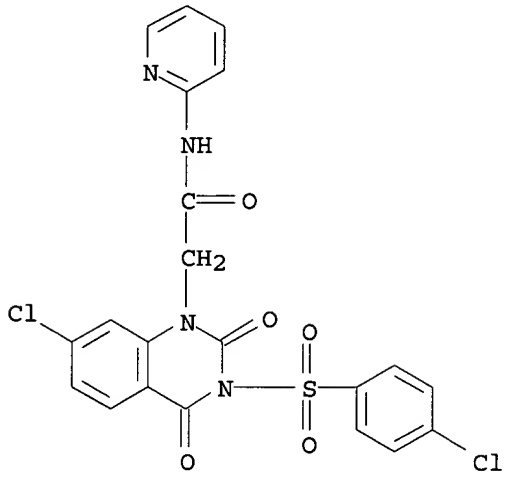


RN 189061-76-5 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-4-pyridinyl- (9CI) (CA INDEX NAME)

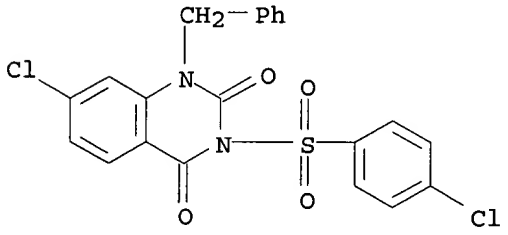


RN 189061-77-6 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-

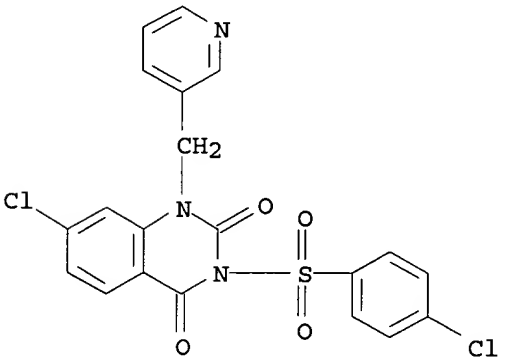
dihydro-2,4-dioxo-N-2-pyridinyl- (9CI) (CA INDEX NAME)



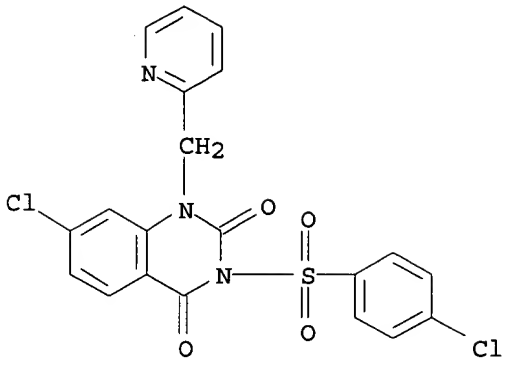
RN 189061-81-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)



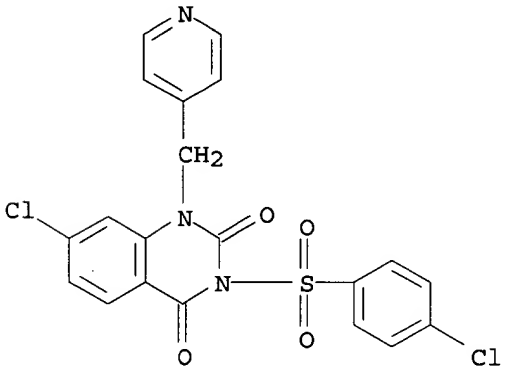
RN 189062-34-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



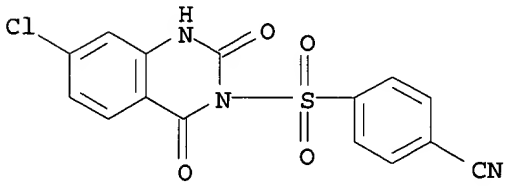
RN 189062-35-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(2-pyridinylmethyl)- (9CI) (CA INDEX NAME)



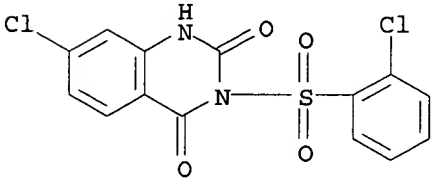
RN 189062-36-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)



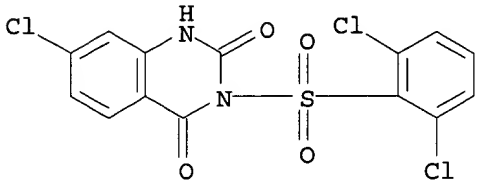
RN 189062-46-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-cyanophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



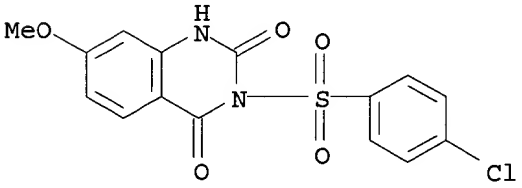
RN 189062-47-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



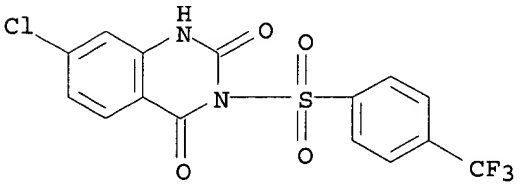
RN 189062-51-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2,6-dichlorophenyl)sulfonyl]-
(9CI) (CA INDEX NAME)



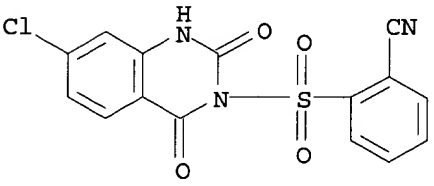
RN 189062-52-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-methoxy- (9CI)
(CA INDEX NAME)



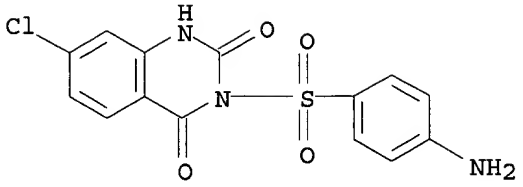
RN 189062-55-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(trifluoromethyl)phenyl]sulfon
yl]- (9CI) (CA INDEX NAME)



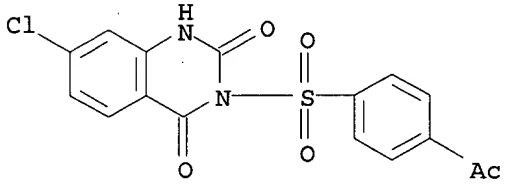
RN 189062-61-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2-cyanophenyl)sulfonyl]- (9CI)
(CA INDEX NAME)



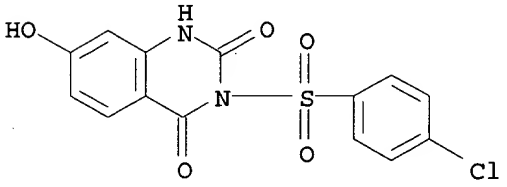
RN 189062-66-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI)
(CA INDEX NAME)



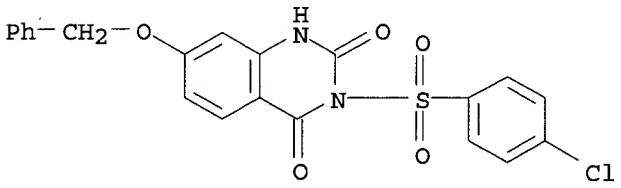
RN 189062-67-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-acetylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



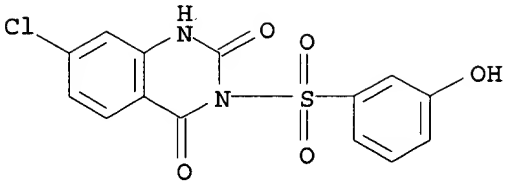
RN 189062-69-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-hydroxy- (9CI) (CA INDEX NAME)



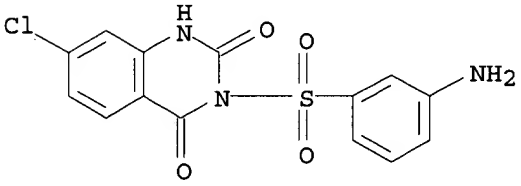
RN 189062-70-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-(phenylmethoxy)- (9CI) (CA INDEX NAME)



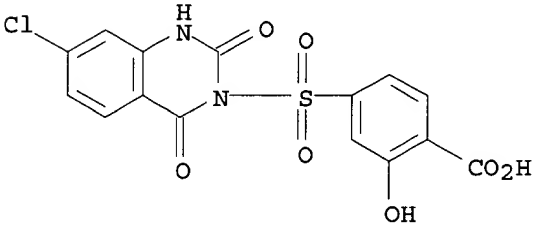
RN 259536-59-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



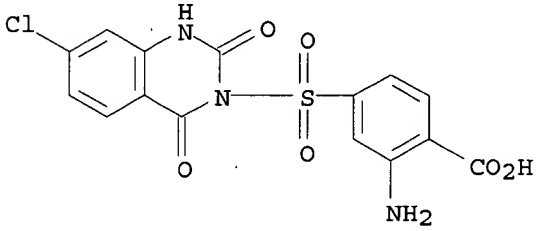
RN 259536-69-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



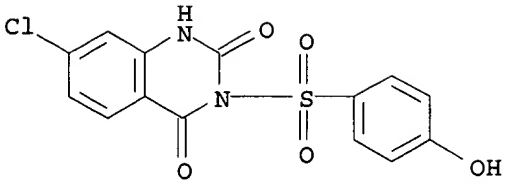
RN 259536-72-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



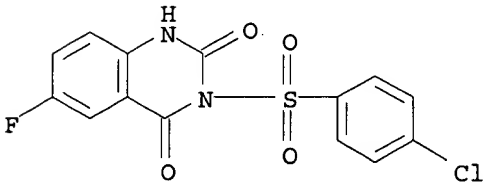
RN 259536-74-8 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



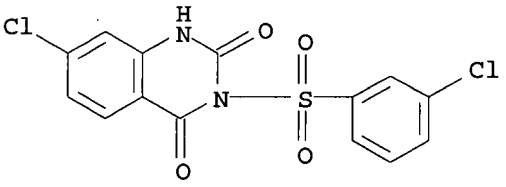
RN 259536-76-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



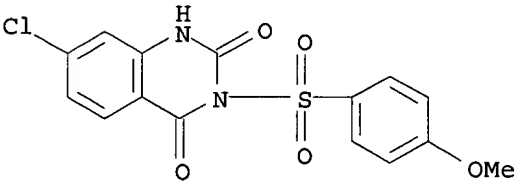
RN 294865-37-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6-fluoro- (9CI) (CA INDEX NAME)



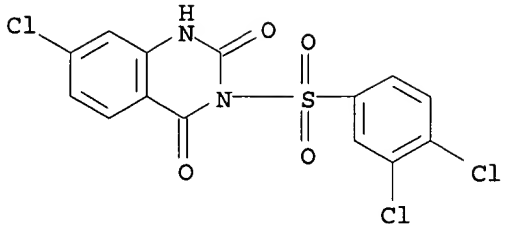
RN 294865-38-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



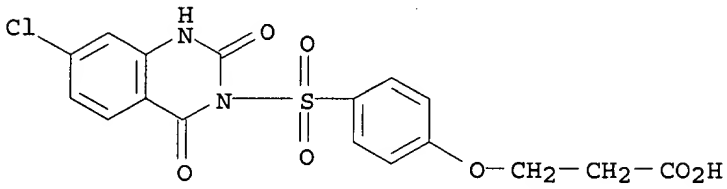
RN 294865-39-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-methoxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 294865-40-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3,4-dichlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)

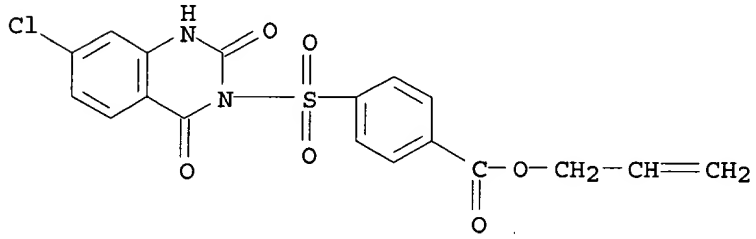


RN 294865-41-1 CAPLUS
CN Propanoic acid, 3-[4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenoxy]- (9CI) (CA INDEX NAME)

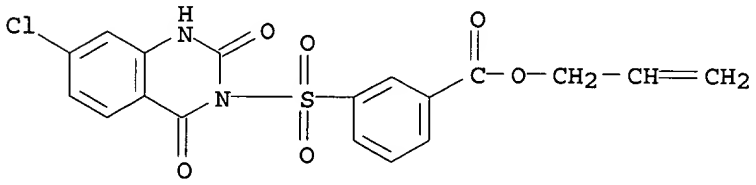


IT **189061-14-1P 189061-33-4P 189061-49-2P 189062-57-5P 259537-02-5P 294865-42-2P 294865-43-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(substituted phenylsulfonylquinazolinedione derivs. as novel nonpeptide inhibitors of human heart chymase in relation to structure and inhibition of chymotrypsin and cathepsin G)

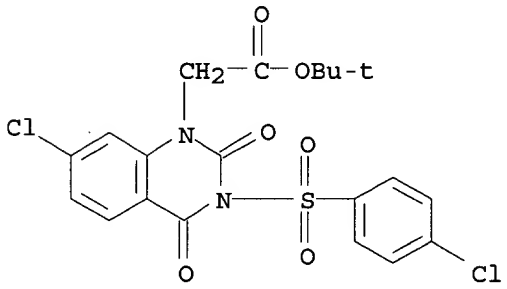
RN 189061-14-1 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)



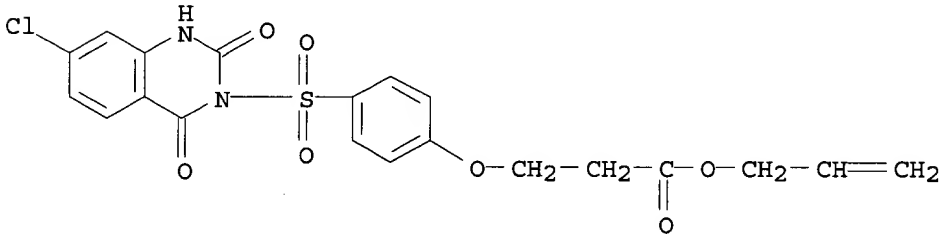
RN 189061-33-4 CAPLUS
CN Benzoic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)



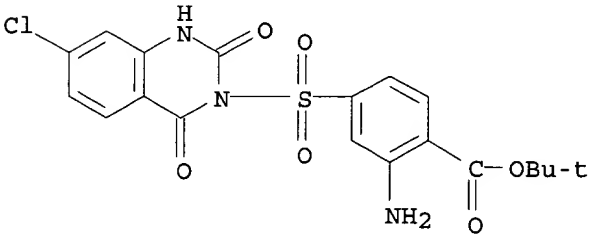
RN 189061-49-2 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



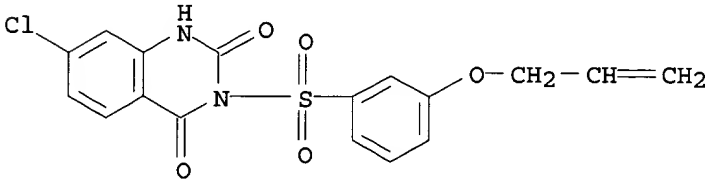
RN 189062-57-5 CAPLUS
CN Propanoic acid, 3-[4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenoxy]-, 2-propenyl ester (9CI) (CA INDEX NAME)



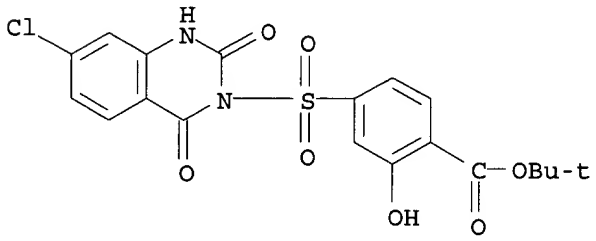
RN 259537-02-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 294865-42-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[3-(2-propenyloxy)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 294865-43-3 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

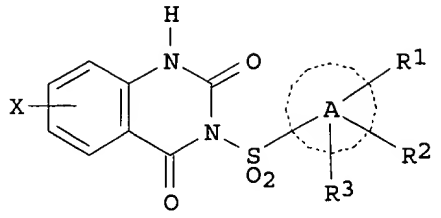


REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

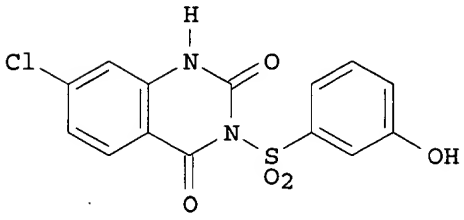
L11 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:144865 CAPLUS
DOCUMENT NUMBER: 132:180595
TITLE: Preparation of quinazoline derivatives as chymase inhibitors
INVENTOR(S): Fukami, Harukazu; Ito, Akiko; Imajo, Seiichi
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000010982	A1	20000302	WO 1999-JP4503	19990820
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953037	A1	20000314	AU 1999-53037	19990820
EP 1114035	A1	20010711	EP 1999-938565	19990820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002523404	T2	20020730	JP 2000-566256	19990820

PRIORITY APPLN. INFO.: JP 1998-235633 A 19980821
WO 1999-JP4503 W 19990820
OTHER SOURCE(S): MARPAT 132:180595
GI



I



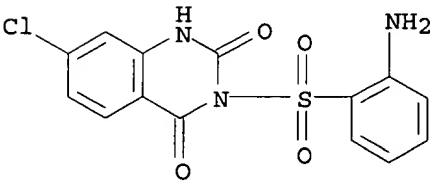
II

AB The title compds. [I; A = aryl; R1 = OH, NH2, alkylamino, etc.; R2, R3 = H, alkyl, halo, etc.; X = H, alkyl, alkoxy, etc.] which have a chymase inhibitory activity and suppress the exacerbation of vascular permeability induced by chymase, were prepd. and formulated. E.g., a 3-step synthesis of II which showed IC50 of 0.36 .mu.M against chymase, was given.

IT **259536-60-2P 259536-69-1P 259536-72-6P**
259536-74-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of quinazolines as chymase inhibitors)

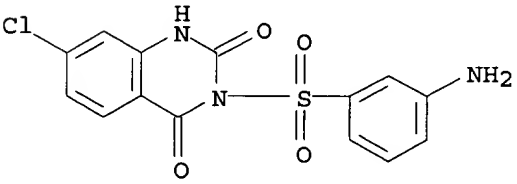
RN 259536-60-2 CAPLUS

CN 2,4(1H,3H)-Quinazolinedione, 3-[(2-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)

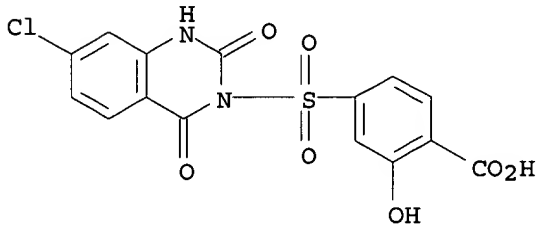


RN 259536-69-1 CAPLUS

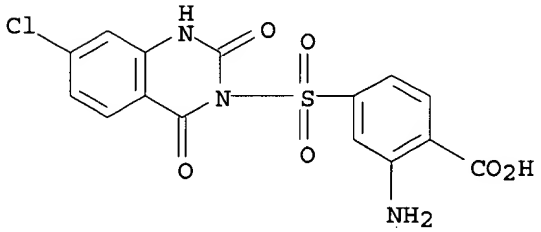
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



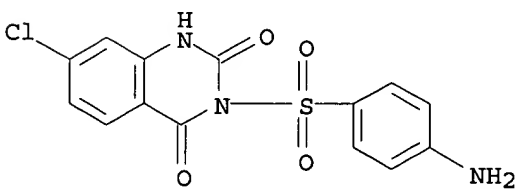
RN 259536-72-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



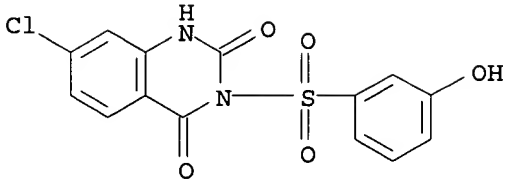
RN 259536-74-8 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



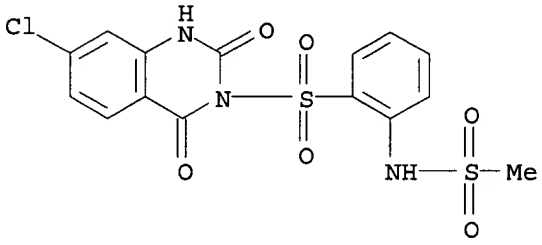
IT **189062-66-6P 259536-59-9P 259536-61-3P**
259536-62-4P 259536-63-5P 259536-64-6P
259536-65-7P 259536-66-8P 259536-67-9P
259536-68-0P 259536-70-4P 259536-71-5P
259536-73-7P 259536-75-9P 259536-76-0P
259536-77-1P 259536-78-2P 259536-79-3P
259536-80-6P 259536-81-7P 259536-82-8P
259536-83-9P 259536-84-0P 259536-85-1P
259536-86-2P 259536-87-3P 259536-88-4P
259536-89-5P 259536-90-8P 259536-91-9P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines as chymase inhibitors)
RN 189062-66-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



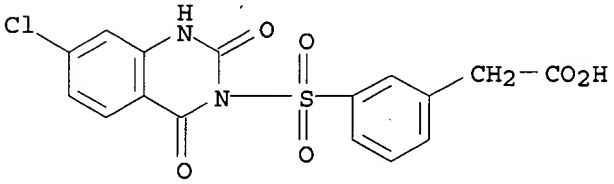
RN 259536-59-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



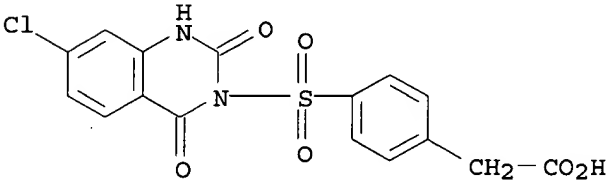
RN 259536-61-3 CAPLUS
CN Methanesulfonamide, N-[2-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



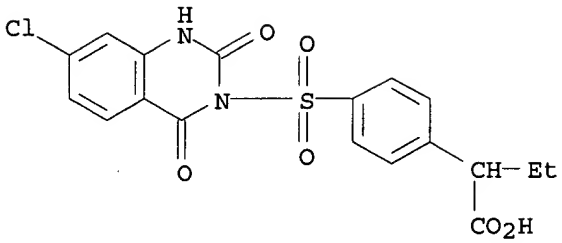
RN 259536-62-4 CAPLUS
CN Benzeneacetic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



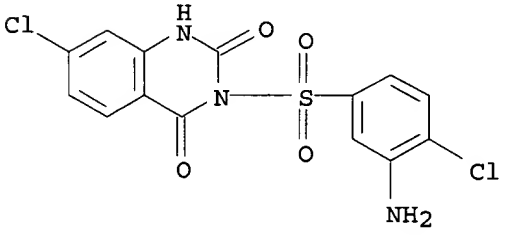
RN 259536-63-5 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



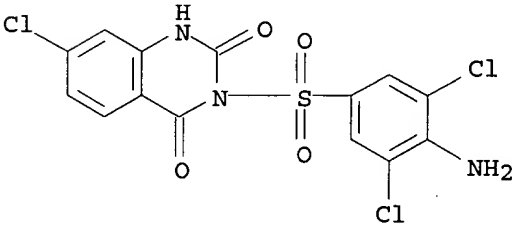
RN 259536-64-6 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl- (9CI) (CA INDEX NAME)



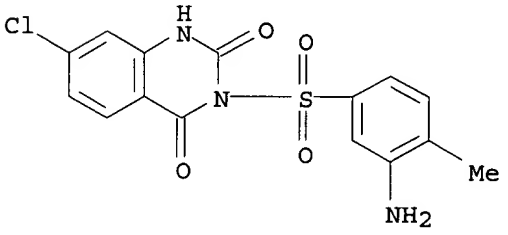
RN 259536-65-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-chlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



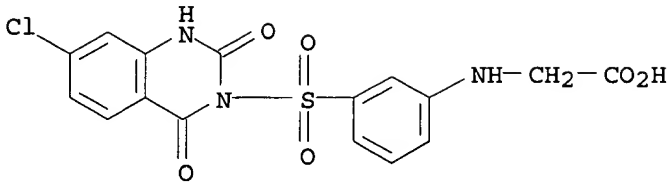
RN 259536-66-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-amino-3,5-dichlorophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



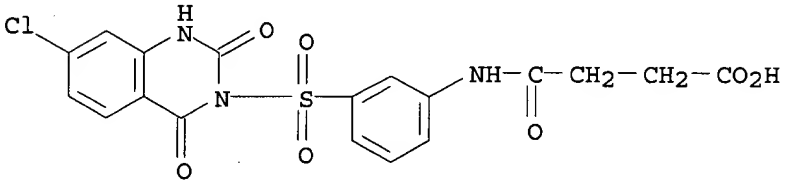
RN 259536-67-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



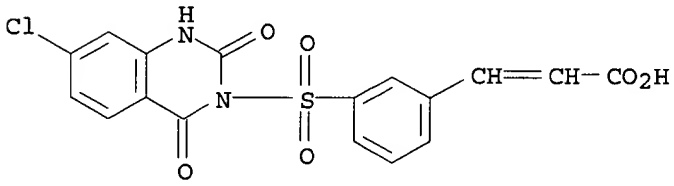
RN 259536-68-0 CAPLUS
CN Glycine, N-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)



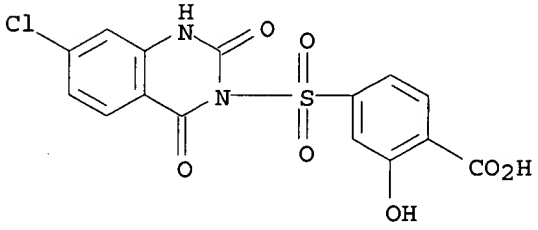
RN 259536-70-4 CAPLUS
CN Butanoic acid, 4-[[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]amino]-4-oxo- (9CI) (CA INDEX NAME)



RN 259536-71-5 CAPLUS
CN 2-Propenoic acid, 3-[3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenyl]- (9CI) (CA INDEX NAME)

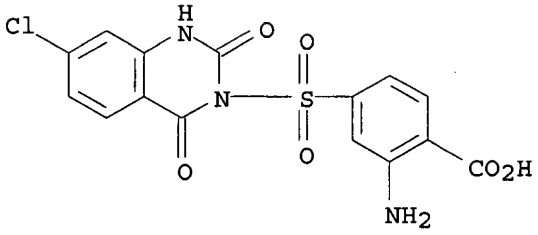


RN 259536-73-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy-, monosodium salt (9CI) (CA INDEX NAME)



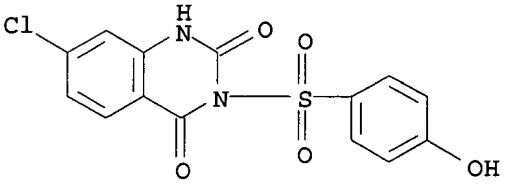
● Na

RN 259536-75-9 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)

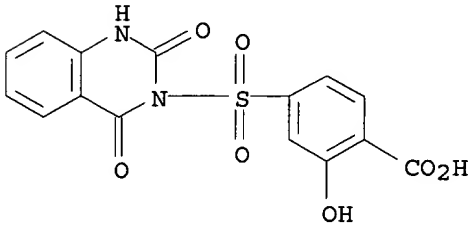


● Na

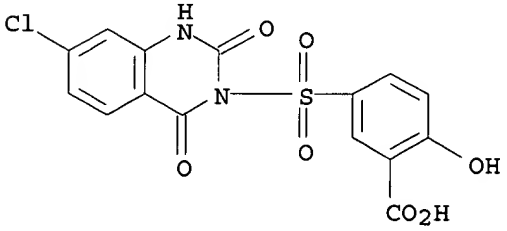
RN 259536-76-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-hydroxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



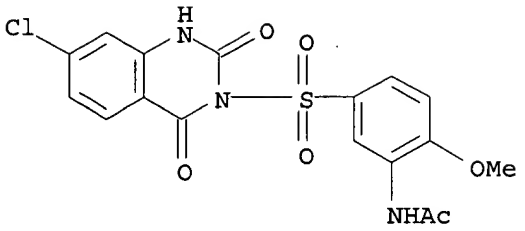
RN 259536-77-1 CAPLUS
CN Benzoic acid, 4-[(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



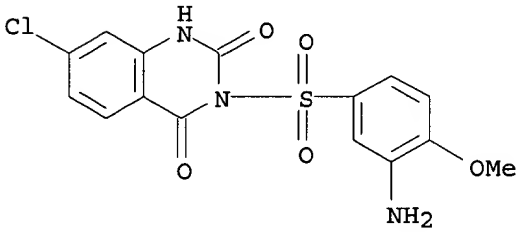
RN 259536-78-2 CAPLUS
CN Benzoic acid, 5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-hydroxy- (9CI) (CA INDEX NAME)



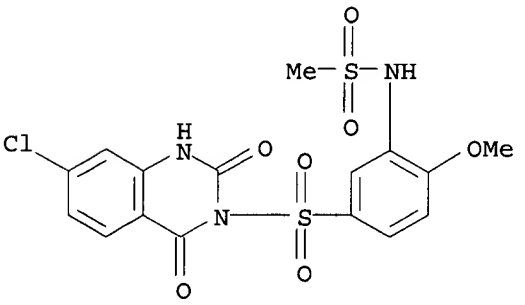
RN 259536-79-3 CAPLUS
CN Acetamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



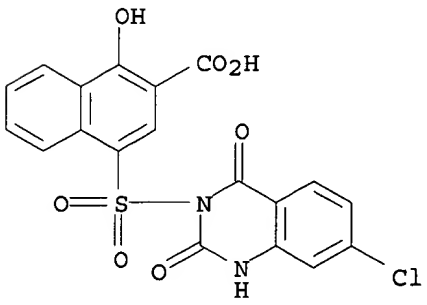
RN 259536-80-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-amino-4-methoxyphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



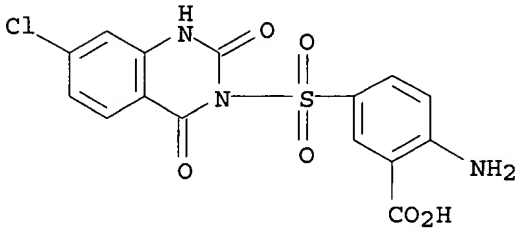
RN 259536-81-7 CAPLUS
CN Methanesulfonamide, N-[5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-methoxyphenyl]- (9CI) (CA INDEX NAME)



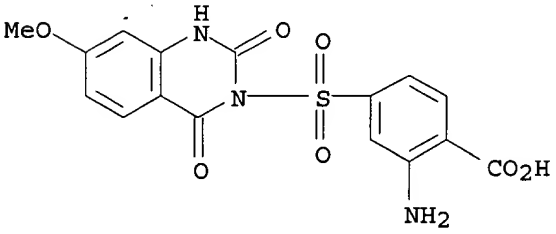
RN 259536-82-8 CAPLUS
CN 2-Naphthalenecarboxylic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1-hydroxy- (9CI) (CA INDEX NAME)



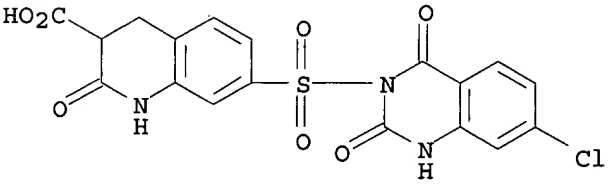
RN 259536-83-9 CAPLUS
CN Benzoic acid, 2-amino-5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



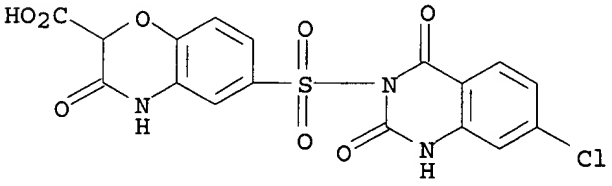
RN 259536-84-0 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-methoxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



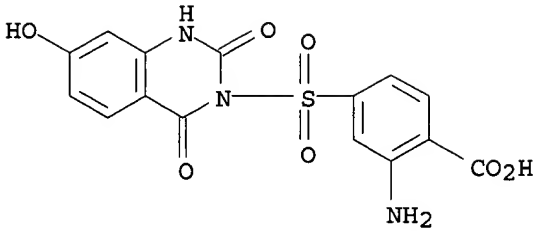
RN 259536-85-1 CAPLUS
CN 3-Quinolinecarboxylic acid, 7-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1,2,3,4-tetrahydro-2-oxo- (9CI) (CA INDEX NAME)



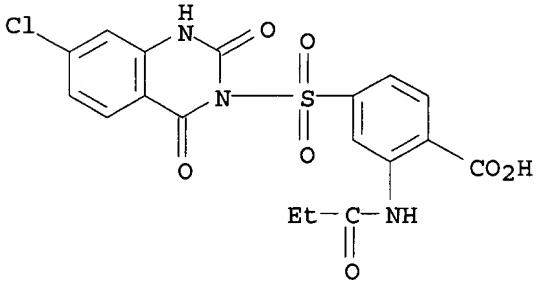
RN 259536-86-2 CAPLUS
CN 2H-1,4-Benzoxazine-2-carboxylic acid, 6-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-3,4-dihydro-3-oxo- (9CI) (CA INDEX NAME)



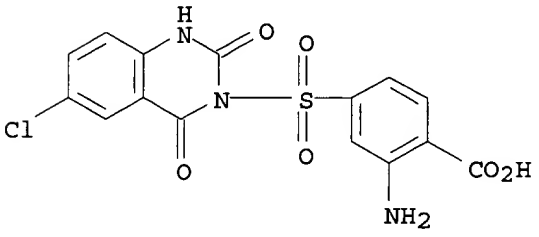
RN 259536-87-3 CAPLUS
CN Benzoic acid, 2-amino-4-[(1,4-dihydro-7-hydroxy-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



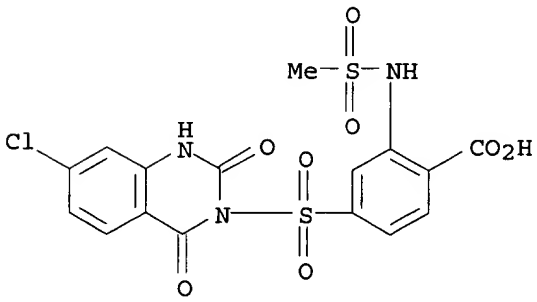
RN 259536-88-4 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(1-oxopropyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-89-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(6-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 259536-90-8 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]- (9CI) (CA INDEX NAME)



RN 259536-91-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(3-aminophenyl)sulfonyl]-7-chloro-, monomethanesulfonate (9CI) (CA INDEX NAME)

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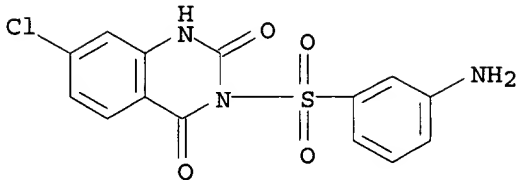
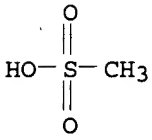
CRN 259536-69-1
CMF C14 H10 Cl N3 O4 S



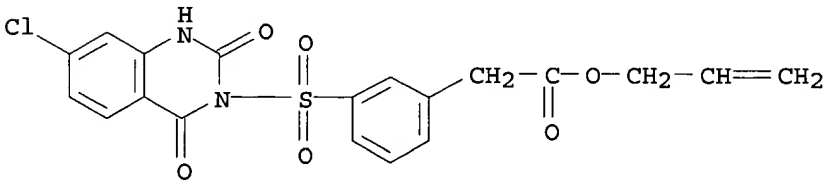
CM 2

CRN 75-75-2
CMF C H4 O3 S

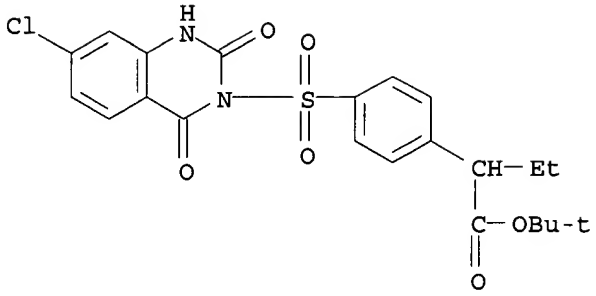


IT **259536-93-1P 259536-95-3P 259537-02-5P**
259537-03-6P 259537-12-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of quinazolines as chymase inhibitors)

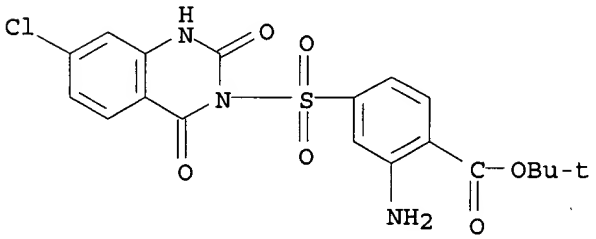
RN 259536-93-1 CAPLUS
CN Benzeneacetic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)



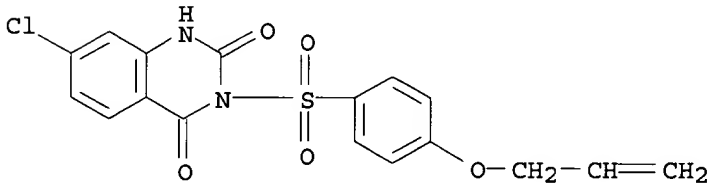
RN 259536-95-3 CAPLUS
CN Benzeneacetic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-.alpha.-ethyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



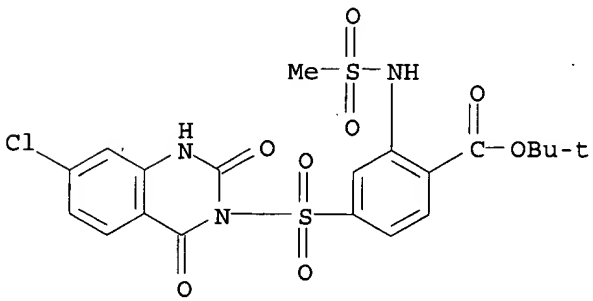
RN 259537-02-5 CAPLUS
CN Benzoic acid, 2-amino-4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 259537-03-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(2-propenyloxy)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 259537-12-7 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-2-[(methylsulfonyl)amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



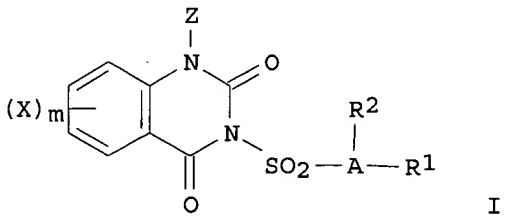
09/ 869,360

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:310799 CAPLUS
DOCUMENT NUMBER: 126:293363
TITLE: Preparation of 2-phenylsulfonyl- and 2-(heterocyclylsulfonyl)quinazoline derivatives as chymase inhibitors
INVENTOR(S): Fukami, Harukazu; Ito, Akiko; Niwata, Shinjiro; Kakutani, Saki; Sumida, Motoo; Kiso, Yoshinobu
PATENT ASSIGNEE(S): Suntory Limited, Japan; Fukami, Harukazu; Ito, Akiko; Niwata, Shinjiro; Kakutani, Saki; Sumida, Motoo; Kiso, Yoshinobu
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9711941	A1	19970403	WO 1996-JP2830	19960927
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 795548	A1	19970917	EP 1996-932039	19960927
EP 795548	B1	20020703		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5814631	A	19980929	US 1997-849114	19970528

PRIORITY APPLN. INFO.: JP 1995-285437 A 19950928
JP 1996-116557 A 19960510
WO 1996-JP2830 W 19960927
OTHER SOURCE(S): MARPAT 126:293363
GI



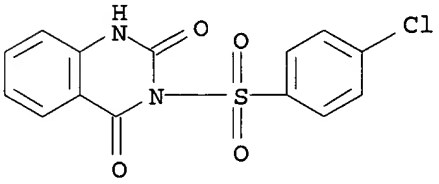
I

AB Quinazoline derivs. represented by general formula [I; group A = benzene, pyridine, pyrrole, or pyrazole ring; m = 0-2; X = OH, NO2, halo, C1-4 (halo)alkyl, or (halo)alkoxy, C7-12 aralkyloxy; X = group to form a naphthalene or quinoline ring together with the benzene ring to which X is attached; R1, R2 = H, halo, C1-4 (halo)alkyl, NO2, cyano, pyrazolyl, tetrazolyl, C1-4 alkyl, CO2H, allyloxycarbonyl, C1-4 (un)substituted alkoxy; or R1 and R2 together with the benzene ring represent a naphthalene or quinoline ring; Z = H, C1-4 (halo)alkyl, C2-5 alkenyl, (un)substituted aralkyl, arom. heterocyclylalkyl, C1-4 alkoxycarbonylmethyl, allyloxycarbonylmethyl, (1.degree. or 2.degree. amino)carbonylmethyl, (un)substituted aralkyloxymethyl; proviso given] or pharmacol. acceptable salts thereof are prepd. They are useful as preventives/remedies for cardiac and circulatory diseases (e.g. hypertension or heart failure) caused by abnormal overprodn. of

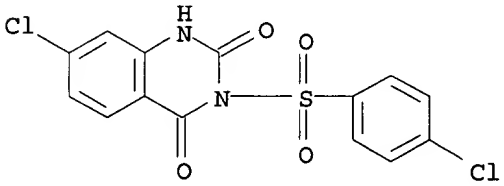
angiotensin II. Thus, a quinazolinedione deriv. (II; R = H) (prepn. given) was condensed with 3-(diethylamino)-1,5-dihydro-2,4,3-benzodioxaphosphepine in the presence of tetrazole in DMF, followed by oxidn. with m-chloroperbenzoic acid in CH2Cl2 and hydrogenolysis over 10% Pd-C in dioxane under H atm. to give II [R = P(O)(OH)2]. II (R = H) and II [R = P(O)(OH)2] showed IC50 of 0.060 and 0.025 .mu.M, resp., for inhibiting human heart chymase. The title compds. I also inhibited cathepsin G and chymotrypsin. Formulation examples contg. I were given.

IT **116445-95-5P 189061-05-0P 189061-49-2P**
189061-53-8P 189061-62-9P 189061-86-7P
189061-88-9P 189061-93-6P 189061-94-7P
189061-95-8P 189061-98-1P 189062-04-2P
189062-10-0P 189062-15-5P 189062-16-6P
189062-18-8P 189062-34-8P 189062-42-8P
189062-43-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of N-phenylsulfonyl- and N-(heterocyclylsulfonyl)quinazoline derivs. as chymase inhibitors for treating heart or circulatory diseases)

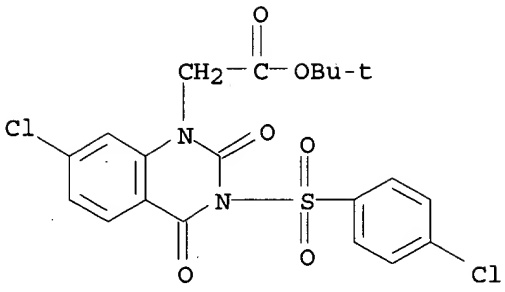
RN 116445-95-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



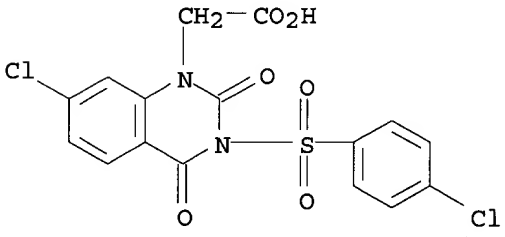
RN 189061-05-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



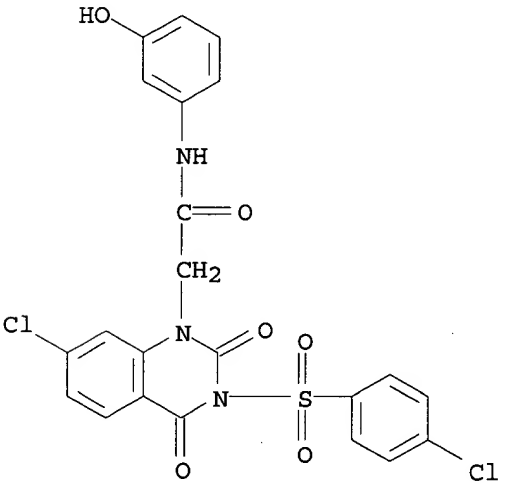
RN 189061-49-2 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



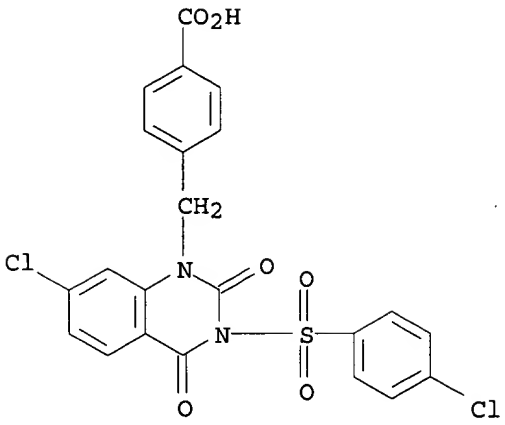
RN 189061-53-8 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)



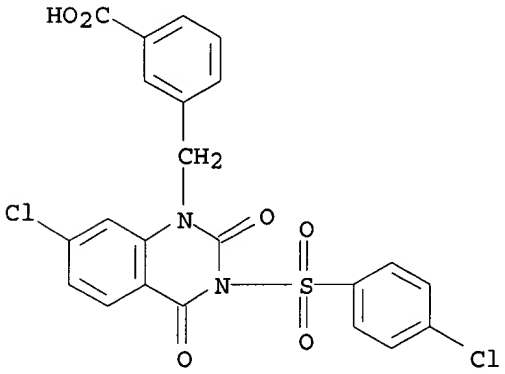
RN 189061-62-9 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-N-(3-hydroxyphenyl)-2,4-dioxo- (9CI) (CA INDEX NAME)



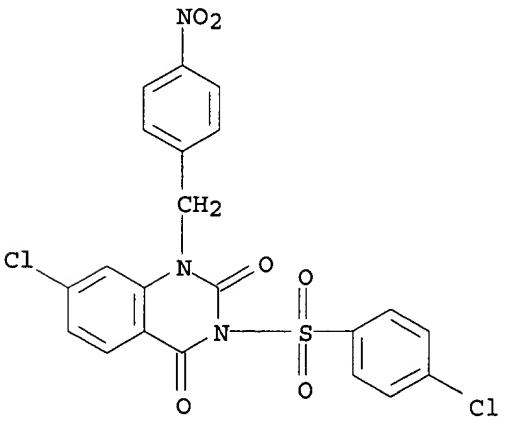
RN 189061-86-7 CAPLUS
CN Benzoic acid, 4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]- (9CI) (CA INDEX NAME)



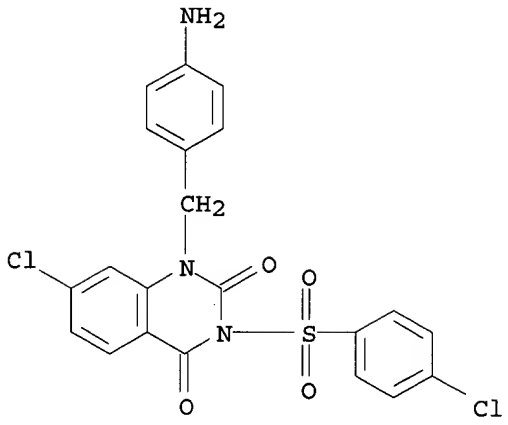
RN 189061-88-9 CAPLUS
CN Benzoic acid, 3-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]- (9CI) (CA INDEX NAME)



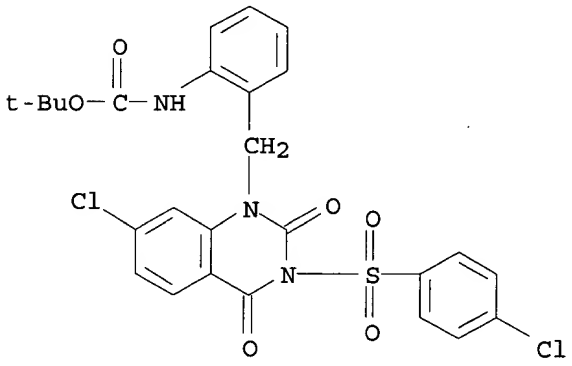
RN 189061-93-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-[(4-nitrophenyl)methyl]- (9CI) (CA INDEX NAME)



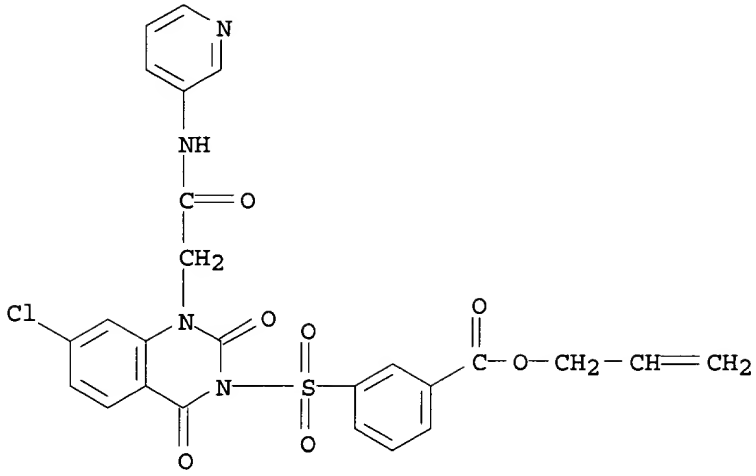
RN 189061-94-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 1-[(4-aminophenyl)methyl]-7-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



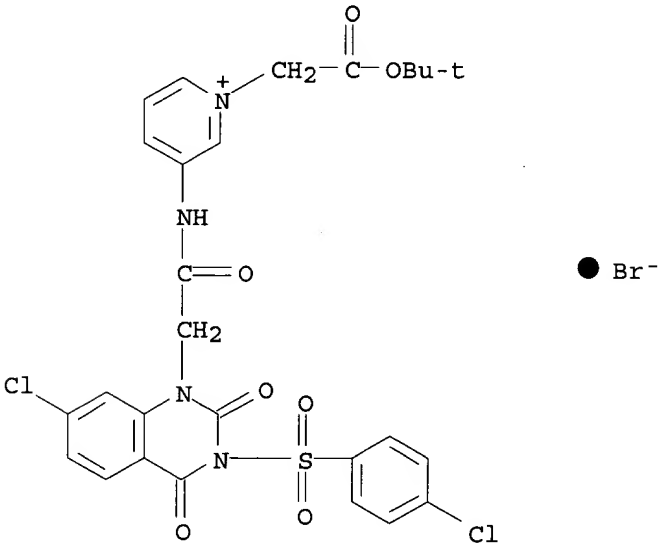
RN 189061-95-8 CAPLUS
CN Carbamic acid, [2-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



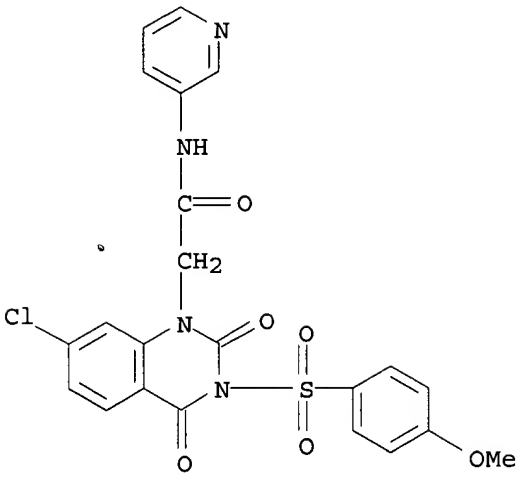
RN 189061-98-1 CAPLUS
CN Benzoic acid, 3-[[7-chloro-1,4-dihydro-2,4-dioxo-1-[2-oxo-2-(3-pyridinylamino)ethyl]-3(2H)-quinazolinyl]sulfonyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)



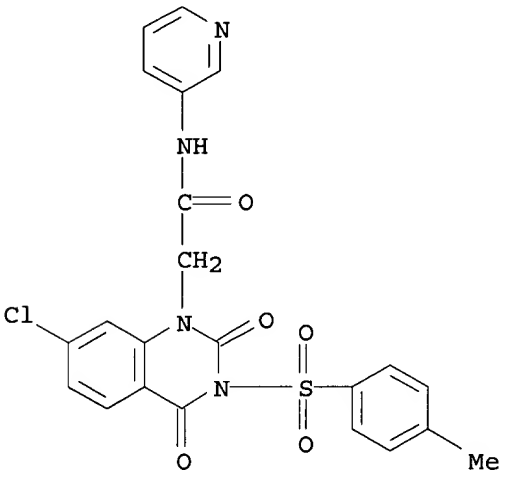
RN 189062-04-2 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-1-[2-(1,1-dimethylethoxy)-2-oxoethyl]-, bromide (9CI) (CA INDEX NAME)



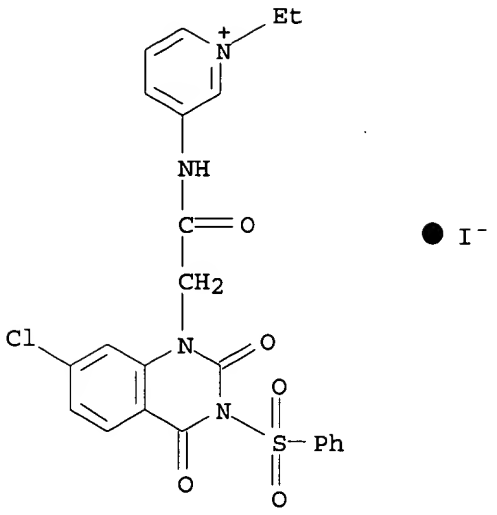
RN 189062-10-0 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3,4-dihydro-3-[(4-methoxyphenyl)sulfonyl]-2,4-dioxo-N-3-pyridinyl- (9CI) (CA INDEX NAME)



RN 189062-15-5 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3,4-dihydro-3-[(4-methylphenyl)sulfonyl]-2,4-dioxo-N-3-pyridinyl- (9CI) (CA INDEX NAME)

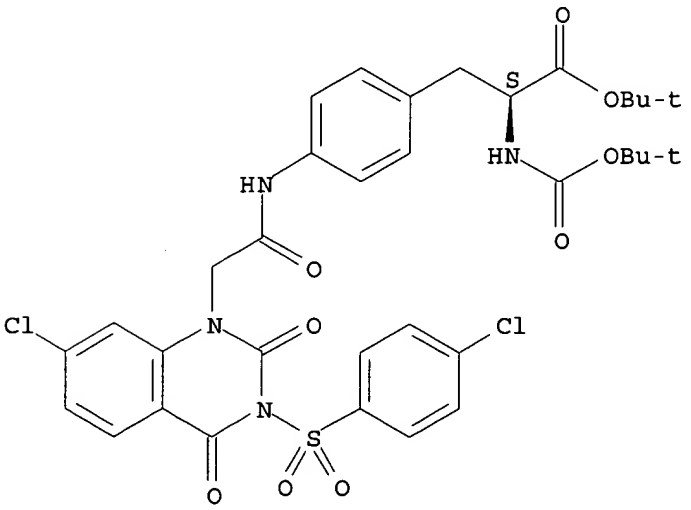


RN 189062-16-6 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3,4-dihydro-2,4-dioxo-3-(phenylsulfonyl)-1(2H)-quinazolinyl]acetyl]amino]-1-ethyl-, iodide (9CI) (CA INDEX NAME)

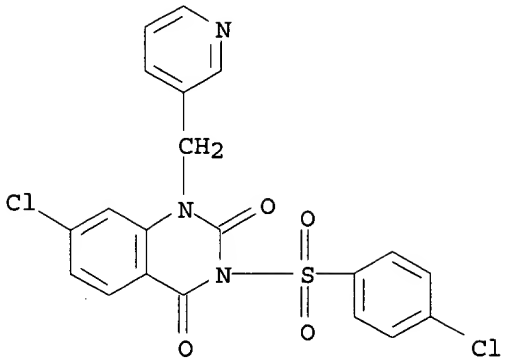


RN 189062-18-8 CAPLUS
CN L-Phenylalanine, 4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-N-[(1,1-dimethylethoxy)carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

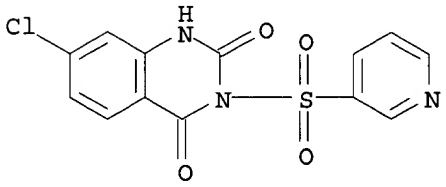
Absolute stereochemistry.



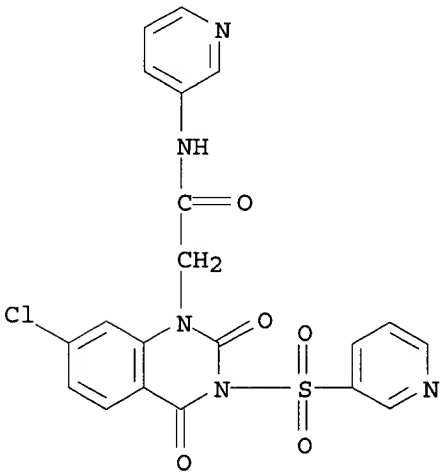
RN 189062-34-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



RN 189062-42-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-(3-pyridinylsulfonyl)- (9CI) (CA INDEX NAME)



RN 189062-43-9 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3,4-dihydro-2,4-dioxo-N-3-pyridinyl-3-(3-pyridinylsulfonyl)- (9CI) (CA INDEX NAME)



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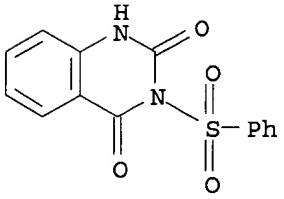
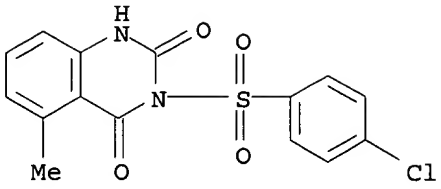
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-phenylsulfonyl- and N-(heterocyclylsulfonyl)quinazoline derivs. as chymase inhibitors for treating heart or circulatory diseases)

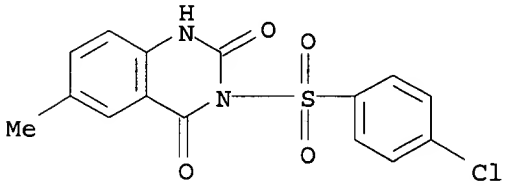
RN 116445-93-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



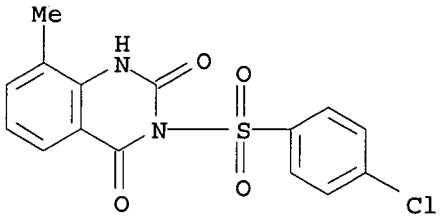
RN 189061-07-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-5-methyl- (9CI) (CA INDEX NAME)



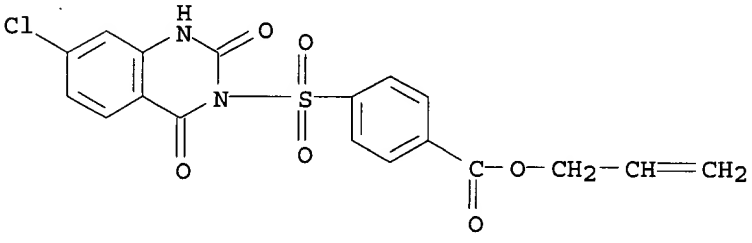
RN 189061-10-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6-methyl- (9CI) (CA INDEX NAME)



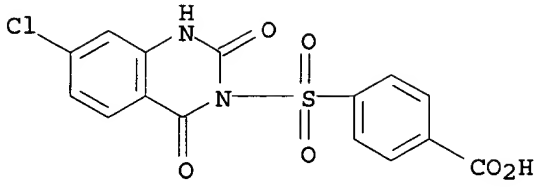
RN 189061-12-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-8-methyl- (9CI) (CA INDEX NAME)



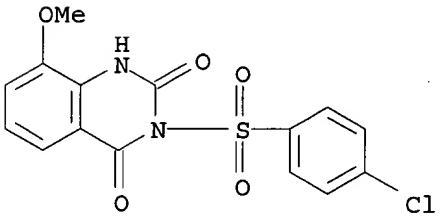
RN 189061-14-1 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)



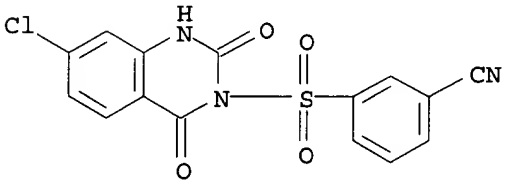
RN 189061-16-3 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



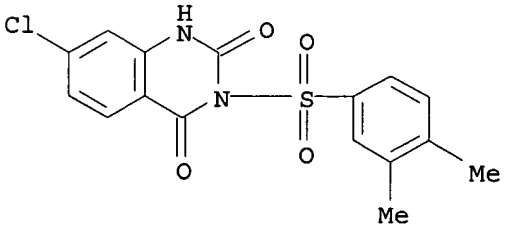
RN 189061-18-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-8-methoxy- (9CI) (CA INDEX NAME)



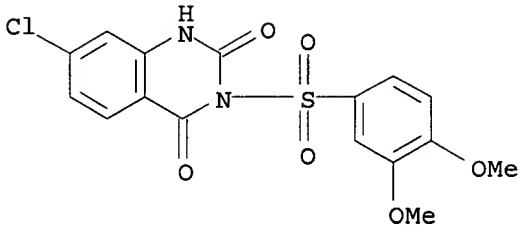
RN 189061-20-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3-cyanophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



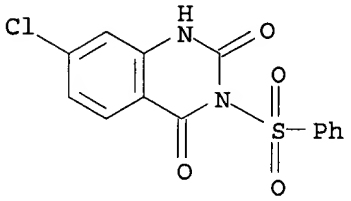
RN 189061-22-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3,4-dimethylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



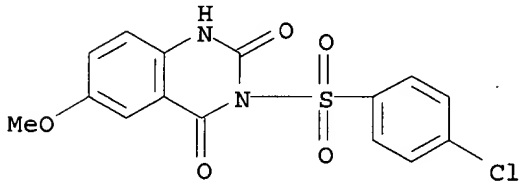
RN 189061-24-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(3,4-dimethoxyphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



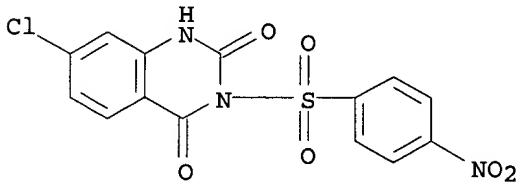
RN 189061-26-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



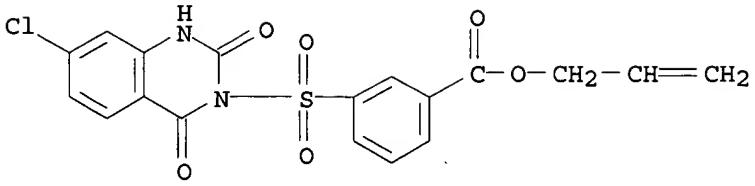
RN 189061-29-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6-methoxy- (9CI) (CA INDEX NAME)



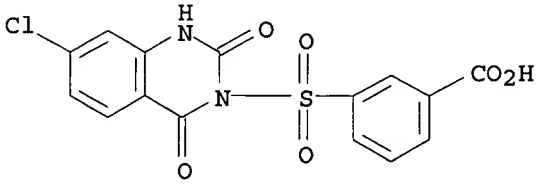
RN 189061-31-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-nitrophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



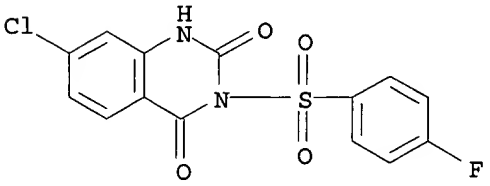
RN 189061-33-4 CAPLUS
CN Benzoic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)



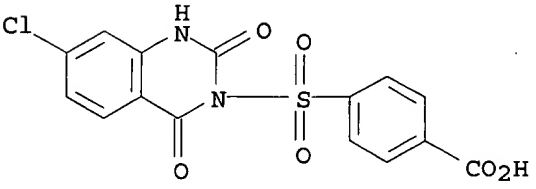
RN 189061-35-6 CAPLUS
CN Benzoic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 189061-37-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-fluorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)

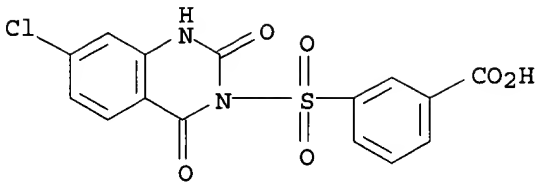


RN 189061-39-0 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)



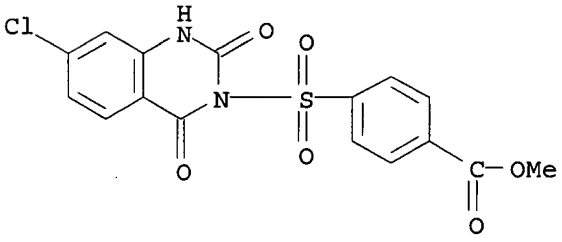
● Na

RN 189061-41-4 CAPLUS
CN Benzoic acid, 3-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, monosodium salt (9CI) (CA INDEX NAME)

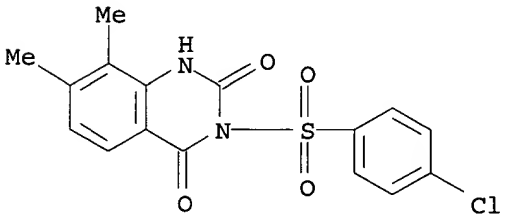


● Na

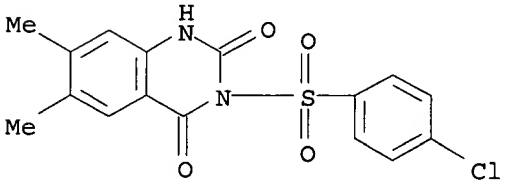
RN 189061-43-6 CAPLUS
CN Benzoic acid, 4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)



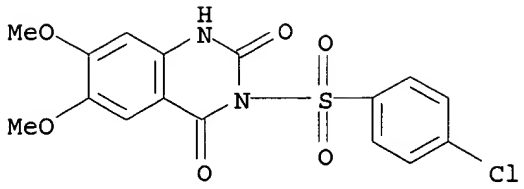
RN 189061-45-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7,8-dimethyl-(9CI) (CA INDEX NAME)



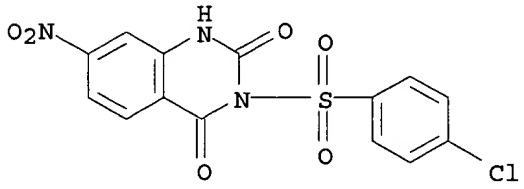
RN 189061-46-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6,7-dimethyl-(9CI) (CA INDEX NAME)



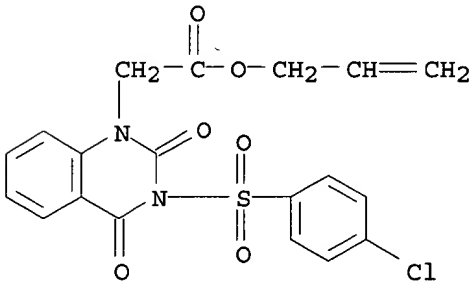
RN 189061-47-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-6,7-dimethoxy-(9CI) (CA INDEX NAME)



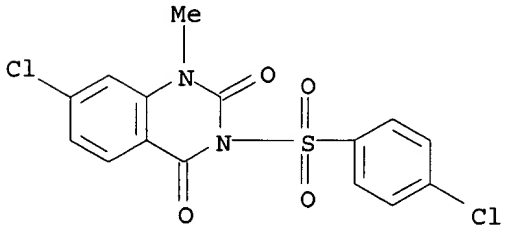
RN 189061-48-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-nitro- (9CI) (CA INDEX NAME)



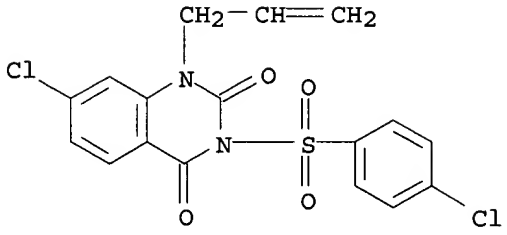
RN 189061-50-5 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-, 2-propenyl ester (9CI) (CA INDEX NAME)



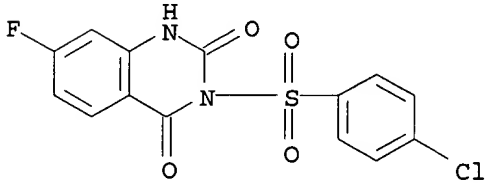
RN 189061-51-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-methyl- (9CI) (CA INDEX NAME)



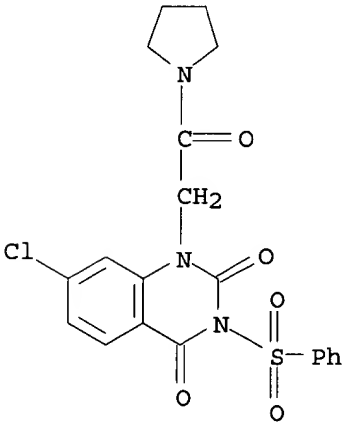
RN 189061-52-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(2-propenyl)- (9CI) (CA INDEX NAME)



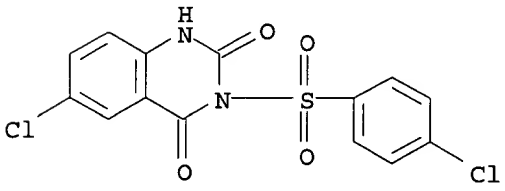
RN 189061-54-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-fluoro- (9CI) (CA INDEX NAME)



RN 189061-55-0 CAPLUS
CN Pyrrolidine, 1-[[7-chloro-3,4-dihydro-2,4-dioxo-3-(phenylsulfonyl)-1(2H)-quinazolinyl]acetyl]- (9CI) (CA INDEX NAME)

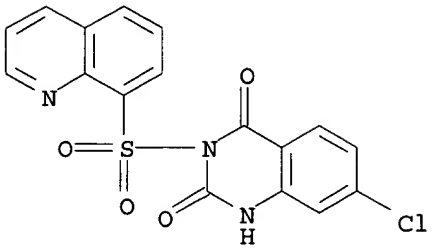


RN 189061-56-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 6-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)

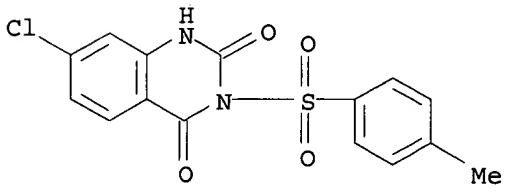


RN 189061-58-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-(8-quinolinylsulfonyl)- (9CI) (CA

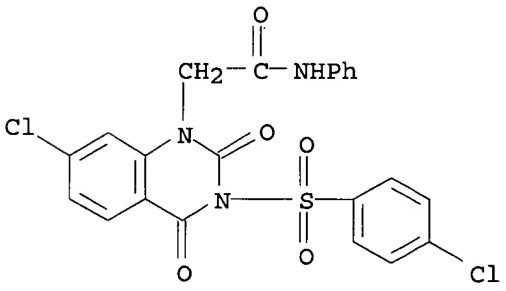
INDEX NAME)



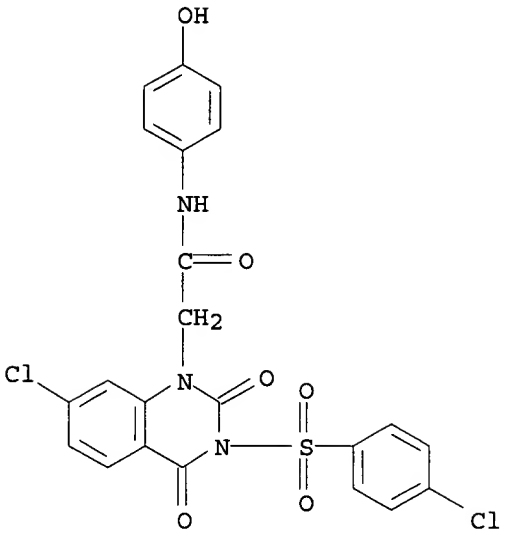
RN 189061-59-4 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



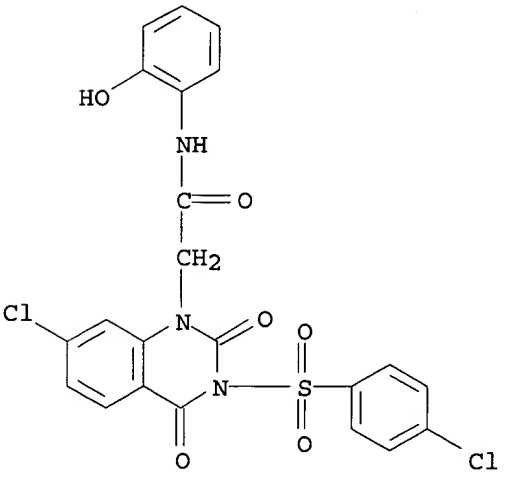
RN 189061-60-7 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-phenyl- (9CI) (CA INDEX NAME)



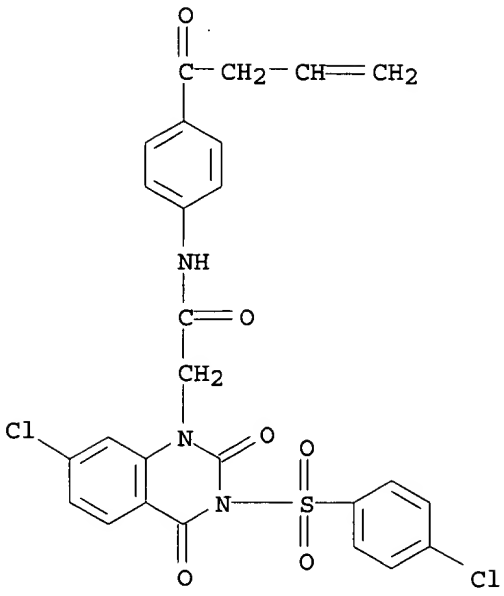
RN 189061-61-8 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-N-(4-hydroxyphenyl)-2,4-dioxo- (9CI) (CA INDEX NAME)



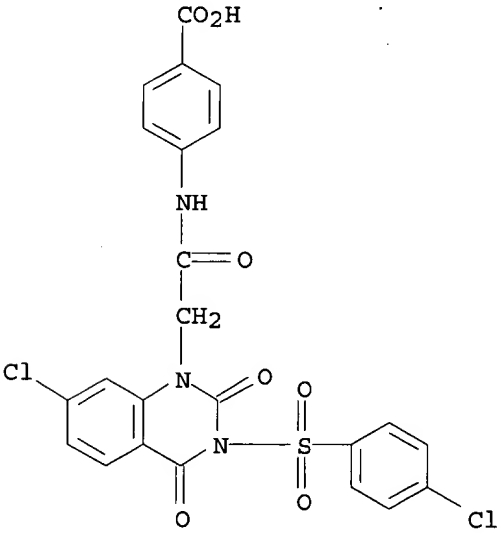
RN 189061-63-0 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-N-(2-hydroxyphenyl)-2,4-dioxo- (9CI) (CA INDEX NAME)



RN 189061-64-1 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-[4-(1-oxo-3-butenyl)phenyl]- (9CI) (CA INDEX NAME)



RN 189061-65-2 CAPLUS
CN Benzoic acid, 4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]- (9CI) (CA INDEX NAME)



RN 189061-66-3 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-N-[4-(4-morpholinylmethyl)phenyl]-2,4-dioxo- (9CI) (CA INDEX NAME)

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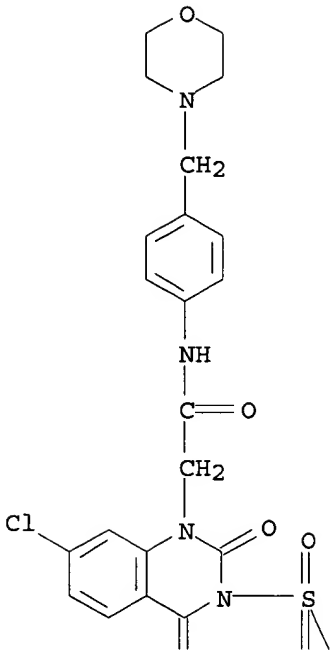
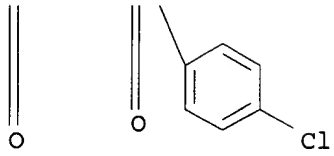
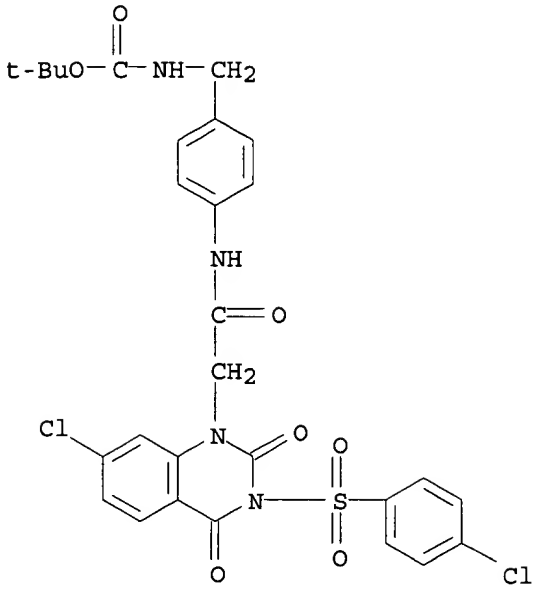


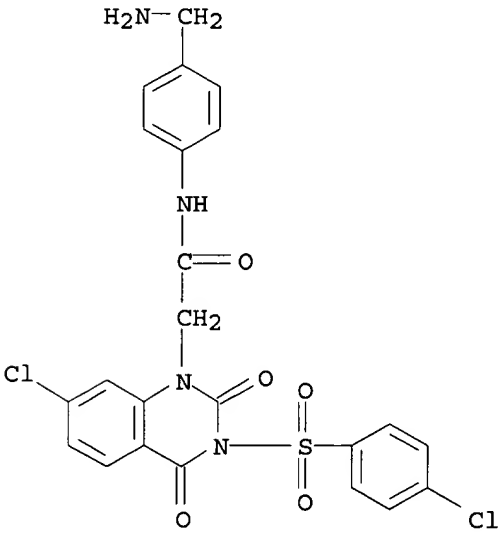
PAGE 2-A



RN 189061-67-4 CAPLUS
CN Carbamic acid, [[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

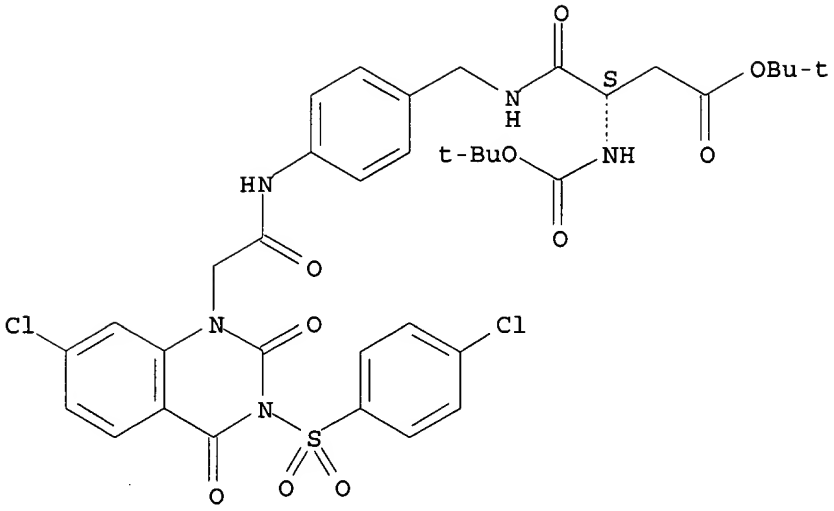


RN 189061-68-5 CAPLUS
CN 1(2H)-Quinazolineacetamide, N-[4-(aminomethyl)phenyl]-7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)



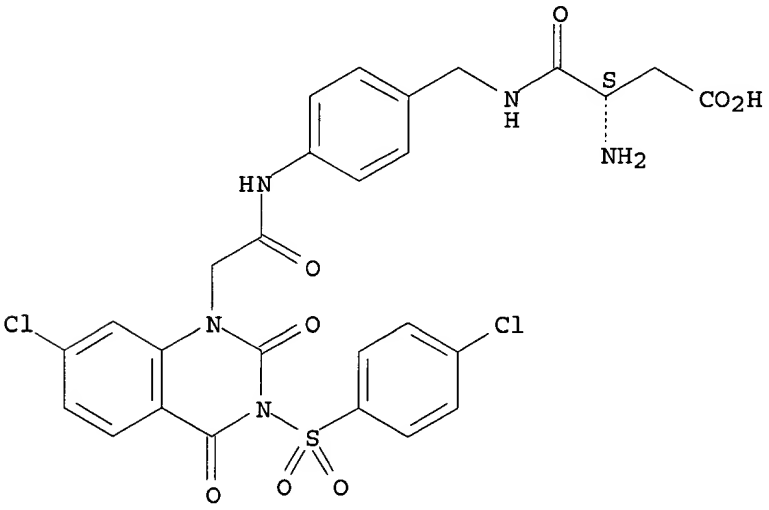
RN 189061-69-6 CAPLUS
CN Butanoic acid, 4-[[[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]amino]-3-[[(1,1-dimethylethoxy)carbonyl]amino]-4-oxo-, 1,1-dimethylethyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



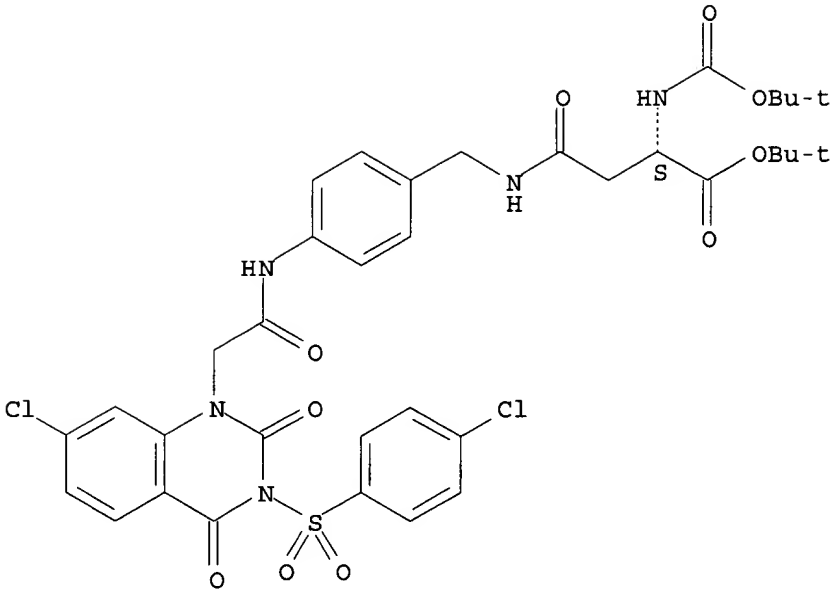
RN 189061-70-9 CAPLUS
CN Butanoic acid, 3-amino-4-[[[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]amino]-4-oxo-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



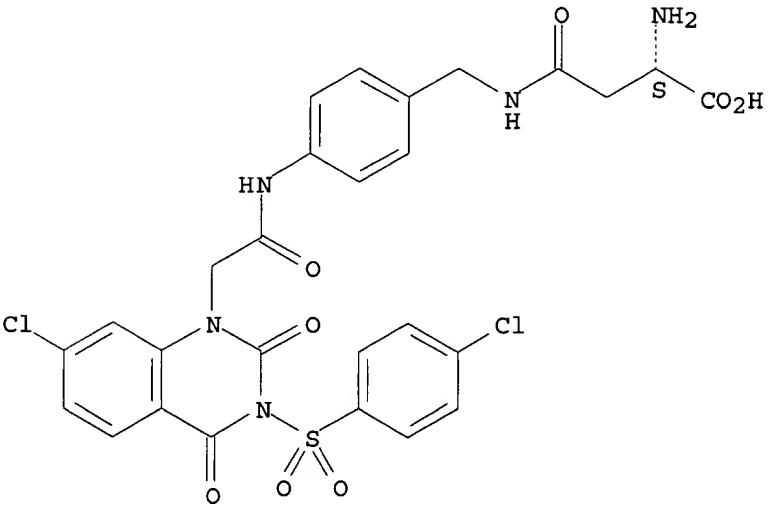
RN 189061-71-0 CAPLUS
CN L-Asparagine, N-[[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]-N2-[(1,1-dimethylethoxy)carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



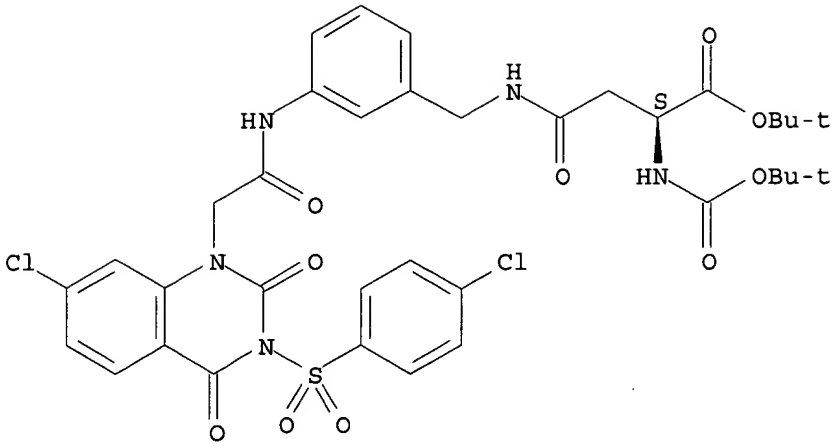
RN 189061-72-1 CAPLUS
CN L-Asparagine, N-[[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



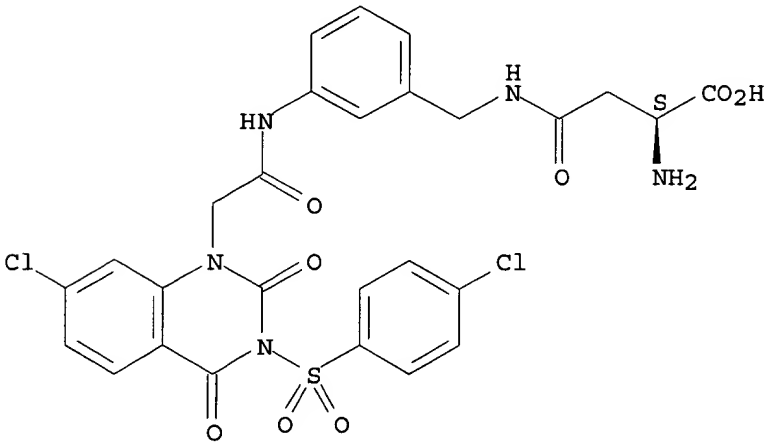
RN 189061-73-2 CAPLUS
CN L-Asparagine, N-[[3-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]-N2-[(1,1-dimethylethoxy)carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

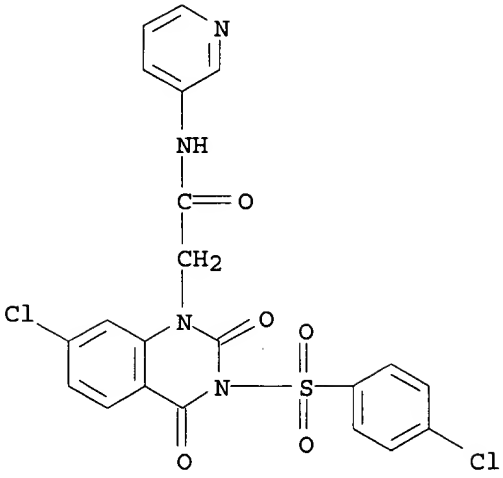


RN 189061-74-3 CAPLUS
CN L-Asparagine, N-[[3-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)

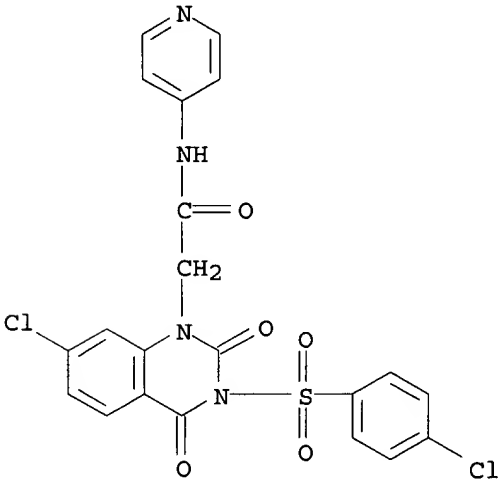
Absolute stereochemistry.



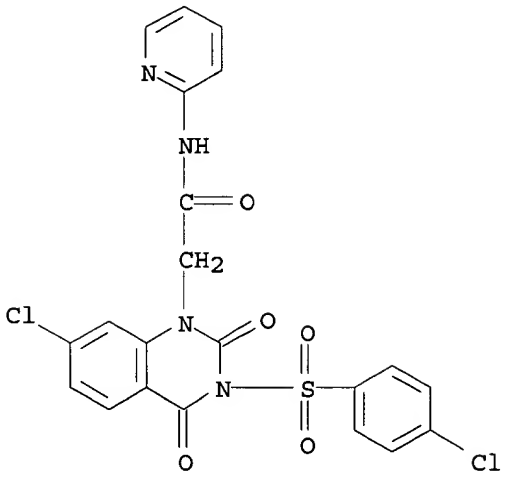
RN 189061-75-4 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-3-pyridinyl- (9CI) (CA INDEX NAME)



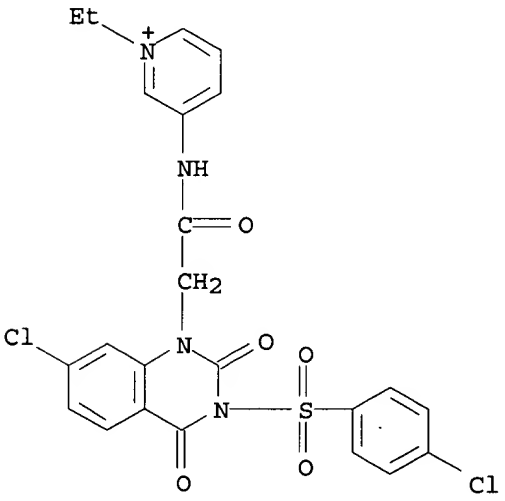
RN 189061-76-5 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-4-pyridinyl- (9CI) (CA INDEX NAME)



RN 189061-77-6 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-2-pyridinyl- (9CI) (CA INDEX NAME)

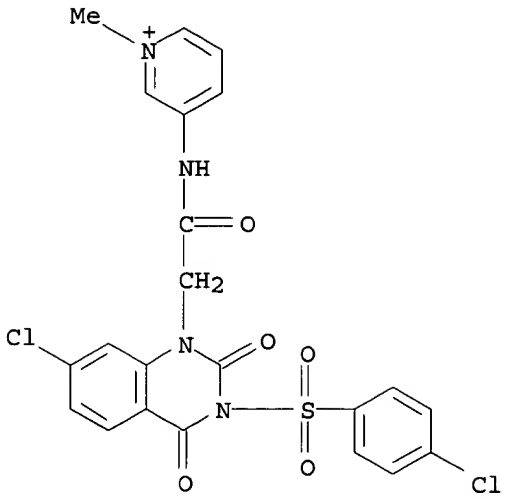


RN 189061-78-7 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-1-ethyl-, iodide (9CI) (CA INDEX NAME)



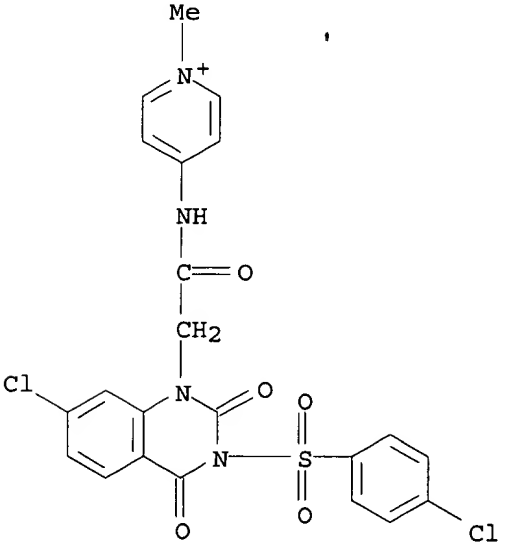
● I⁻

RN 189061-79-8 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-1-methyl-, iodide (9CI) (CA INDEX NAME)



● I^-

RN 189061-80-1 CAPLUS
CN Pyridinium, 4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-1-methyl-, iodide (9CI) (CA INDEX NAME)



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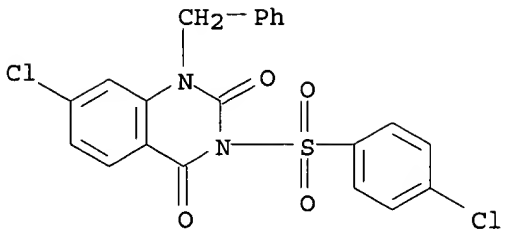
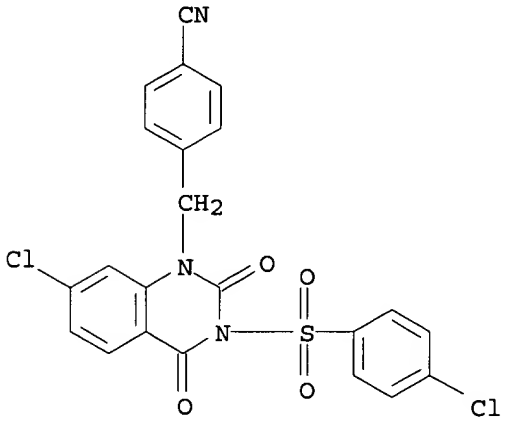
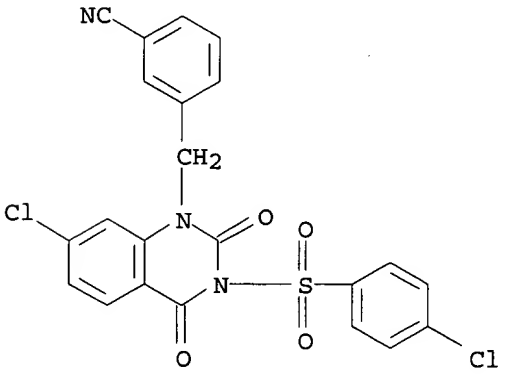
RN 189061-81-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)



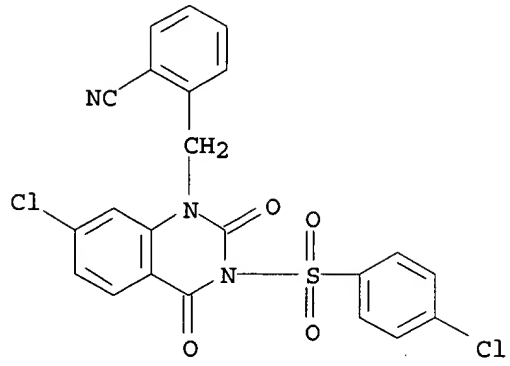
RN 189061-82-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-[(4-cyanophenyl)methyl]- (9CI) (CA INDEX NAME)



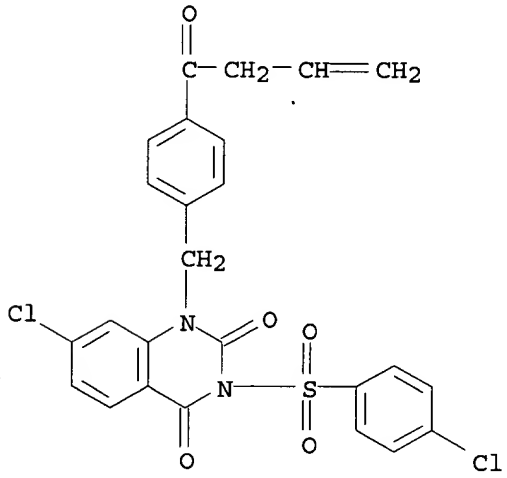
RN 189061-83-4 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-[(3-cyanophenyl)methyl]- (9CI) (CA INDEX NAME)



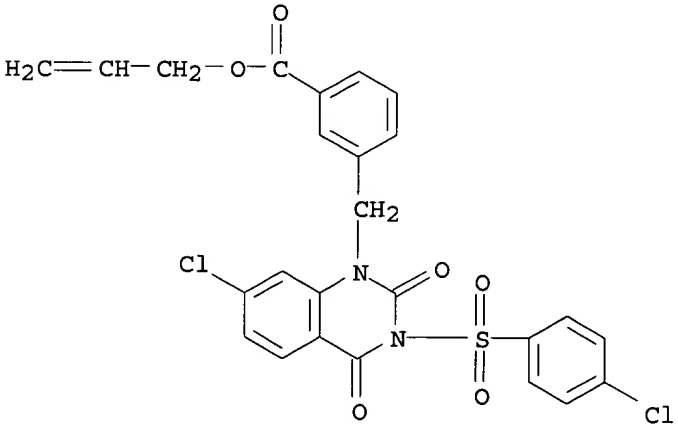
RN 189061-84-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-[(2-cyanophenyl)methyl]- (9CI) (CA INDEX NAME)



RN 189061-85-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-[[4-(1-oxo-3-butenyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

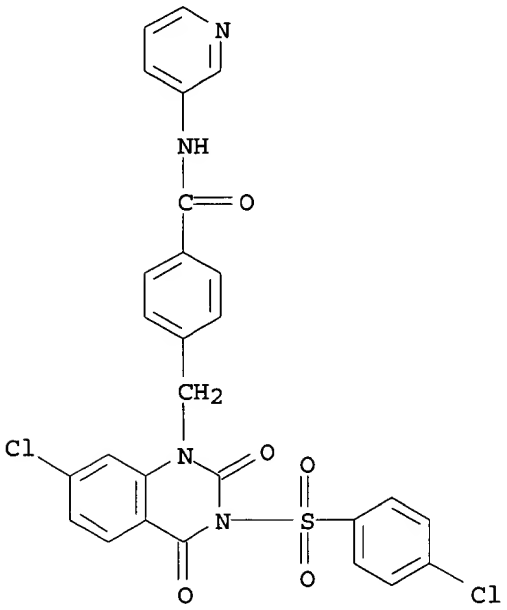


RN 189061-87-8 CAPLUS
CN Benzoic acid, 3-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)

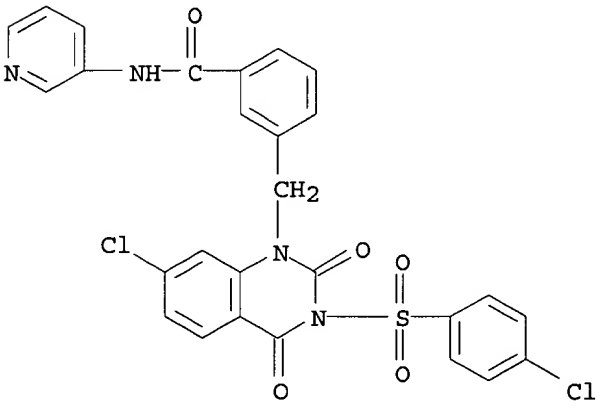


RN 189061-89-0 CAPLUS

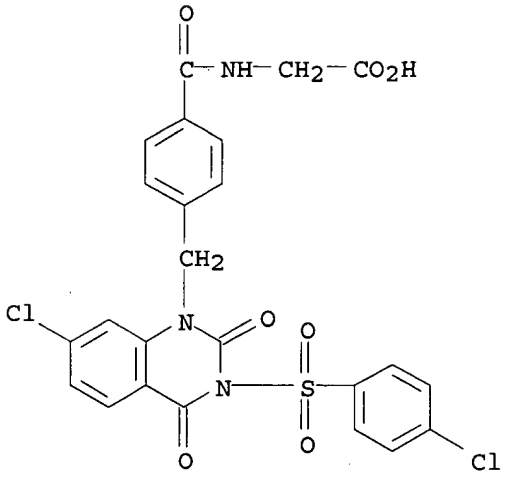
CN Benzamide, 4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-N-3-pyridinyl- (9CI) (CA INDEX NAME)



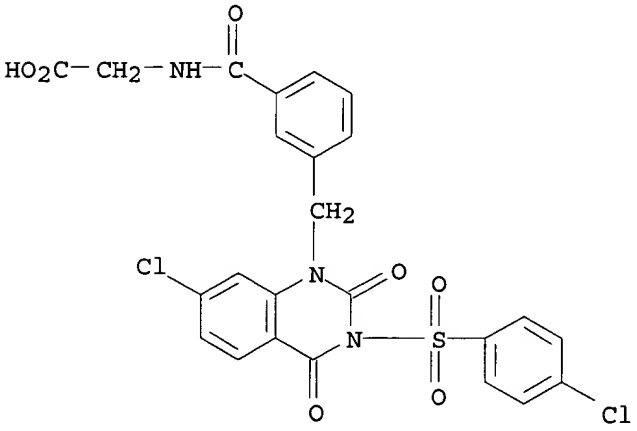
RN 189061-90-3 CAPLUS
CN Benzamide, 3-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-N-3-pyridinyl- (9CI) (CA INDEX NAME)



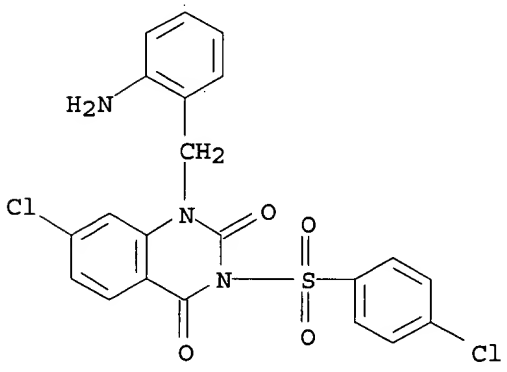
RN 189061-91-4 CAPLUS
CN Glycine, N-[4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]benzoyl]- (9CI) (CA INDEX NAME)



RN 189061-92-5 CAPLUS
CN Glycine, N-[3-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]benzoyl]- (9CI) (CA INDEX NAME)

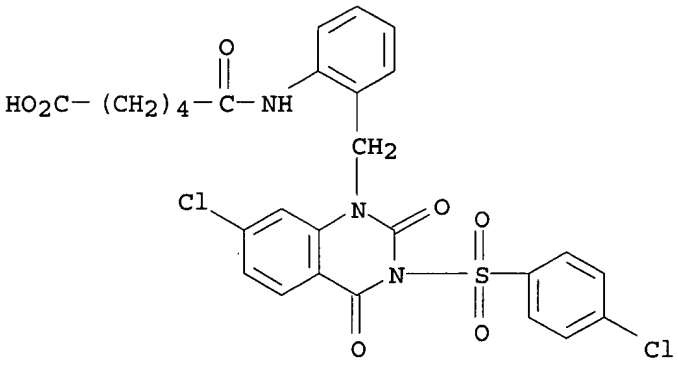


RN 189061-96-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 1-[(2-aminophenyl)methyl]-7-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)

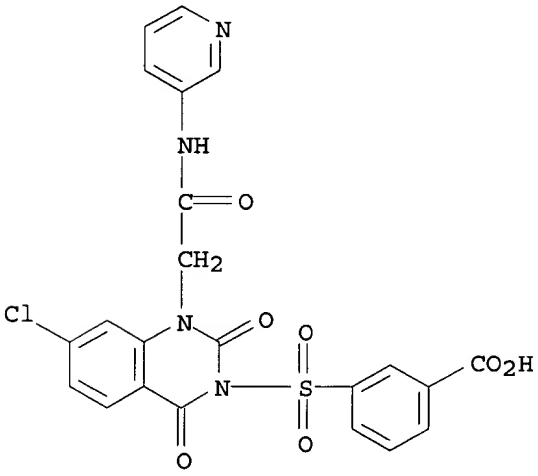


RN 189061-97-0 CAPLUS

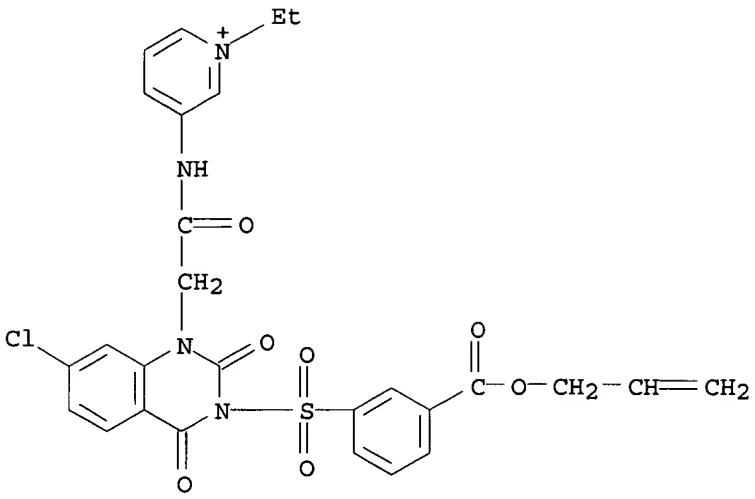
CN Hexanoic acid, 6-[[2-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]phenyl]amino]-6-oxo- (9CI) (CA INDEX NAME)



RN 189061-99-2 CAPLUS
CN Benzoic acid, 3-[[7-chloro-1,4-dihydro-2,4-dioxo-1-[2-oxo-2-(3-pyridinylamino)ethyl]-3(2H)-quinazolinyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 189062-00-8 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3,4-dihydro-2,4-dioxo-3-[[3-[(2-propenyloxy)carbonyl]phenyl]sulfonyl]-1(2H)-quinazolinyl]acetyl]amino]-1-ethyl-, iodide (9CI) (CA INDEX NAME)



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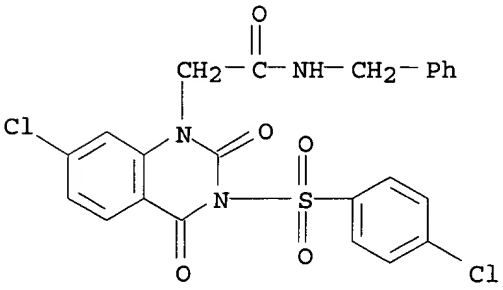
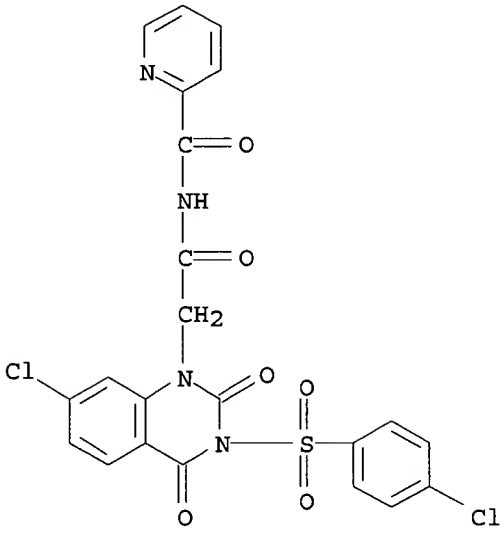
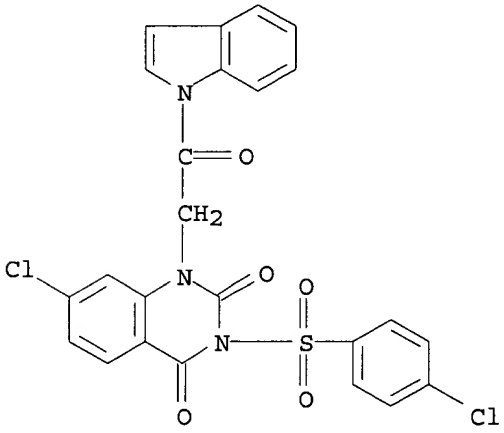
RN 189062-01-9 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



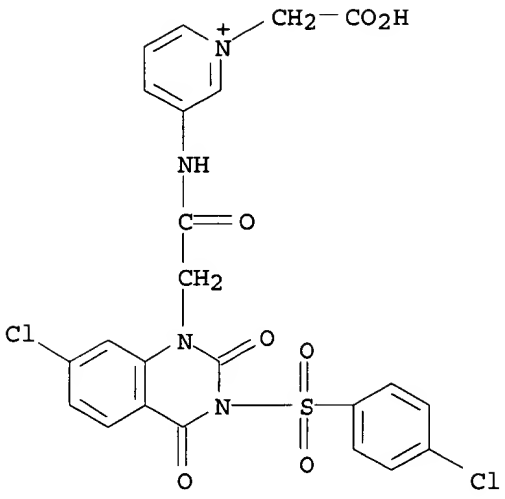
RN 189062-02-0 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-(2-pyridinylcarbonyl)- (9CI) (CA INDEX NAME)



RN 189062-03-1 CAPLUS
CN 1H-Indole, 1-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]- (9CI) (CA INDEX NAME)

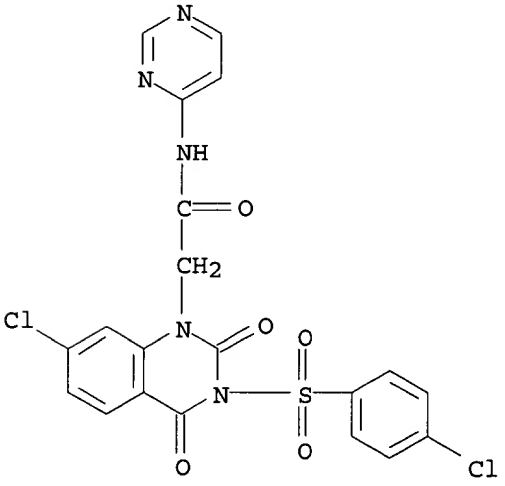


RN 189062-05-3 CAPLUS
CN Pyridinium, 1-(carboxymethyl)-3-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-, bromide (9CI) (CA INDEX NAME)

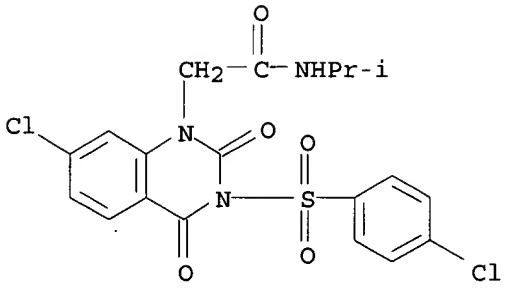


● Br^-

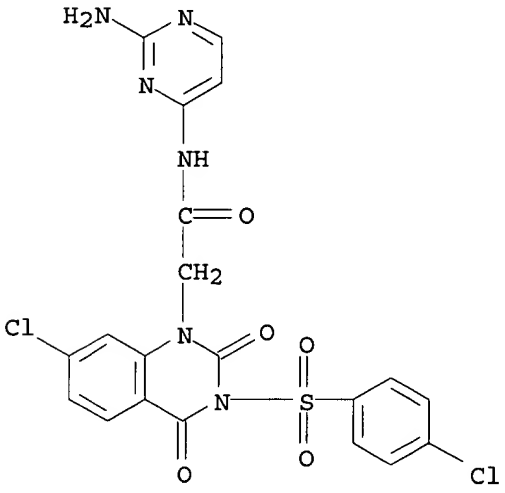
RN 189062-06-4 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-4-pyrimidinyl- (9CI) (CA INDEX NAME)



RN 189062-07-5 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-N-(1-methylethyl)-2,4-dioxo- (9CI) (CA INDEX NAME)

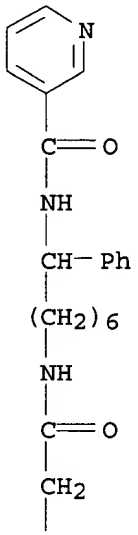


RN 189062-08-6 CAPLUS
CN 1(2H)-Quinazolineacetamide, N-(2-amino-4-pyrimidinyl)-7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)

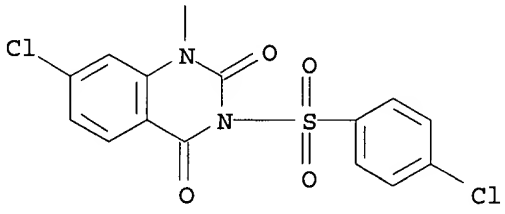


RN 189062-09-7 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-[7-phenyl-7-[(3-pyridinylcarbonyl)amino]heptyl]- (9CI) (CA INDEX NAME)

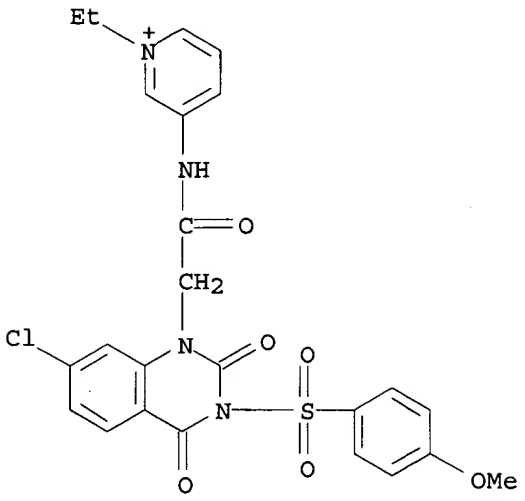
PAGE 1-A



PAGE 2-A



RN 189062-11-1 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3,4-dihydro-3-[(4-methoxyphenyl)sulfonyl]-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-1-ethyl-, iodide (9CI) (CA INDEX NAME)



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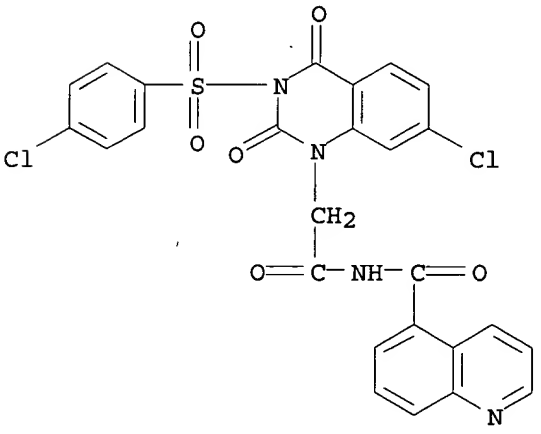
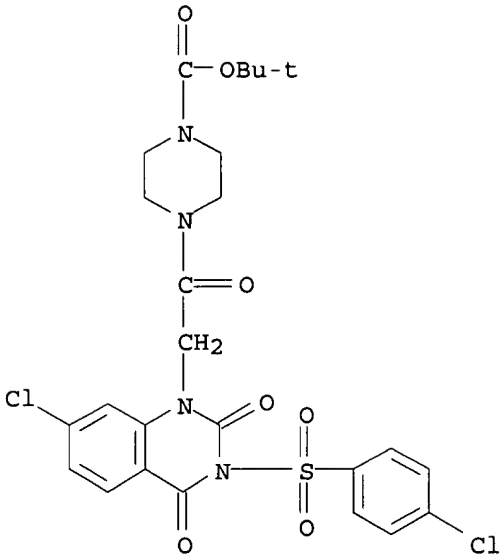
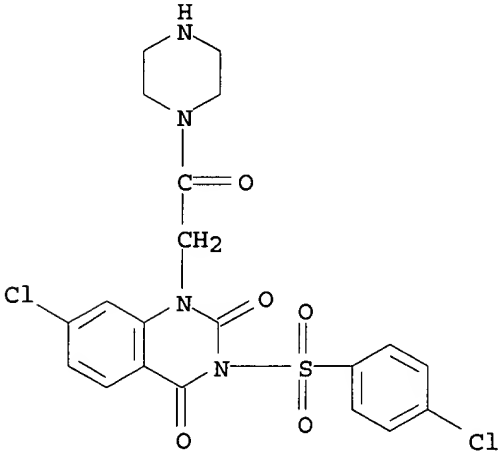
RN 189062-12-2 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-(5-quinolinylcarbonyl)- (9CI) (CA INDEX NAME)



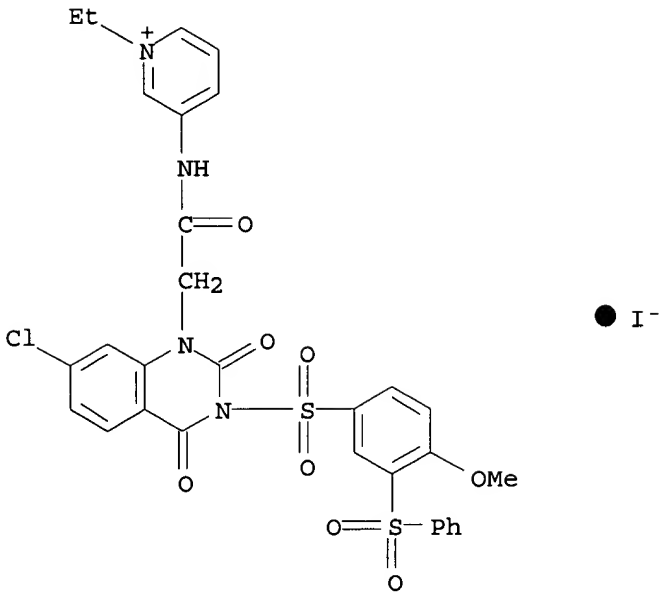
RN 189062-13-3 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 189062-14-4 CAPLUS
CN Piperazine, 1-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]- (9CI) (CA INDEX NAME)

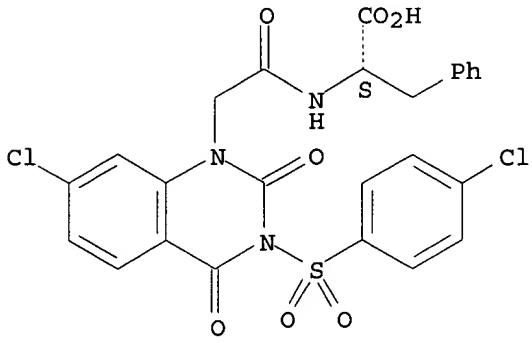


RN 189062-17-7 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3,4-dihydro-3-[[4-methoxy-3-(phenylsulfonyl)phenyl]sulfonyl]-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-1-ethyl-, iodide (9CI) (CA INDEX NAME)

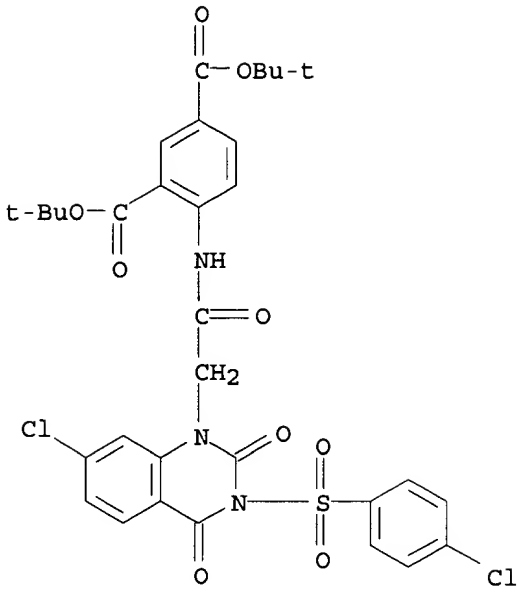


RN 189062-19-9 CAPLUS
CN L-Phenylalanine, N-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]- (9CI) (CA INDEX NAME)

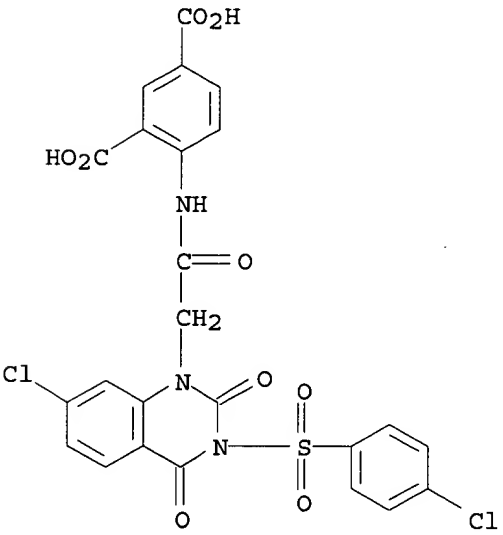
Absolute stereochemistry.



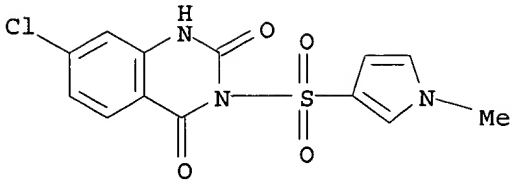
RN 189062-20-2 CAPLUS
CN 1,3-Benzenedicarboxylic acid, 4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



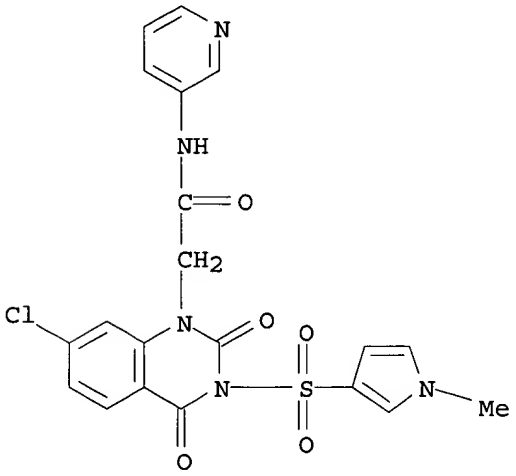
RN 189062-21-3 CAPLUS
CN 1,3-Benzenedicarboxylic acid, 4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]- (9CI) (CA INDEX NAME)



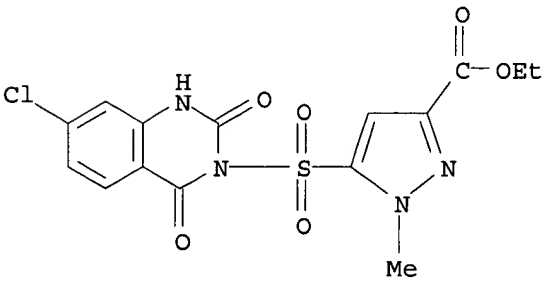
RN 189062-22-4 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(1-methyl-1H-pyrrol-3-yl)sulfonyl]- (9CI) (CA INDEX NAME)



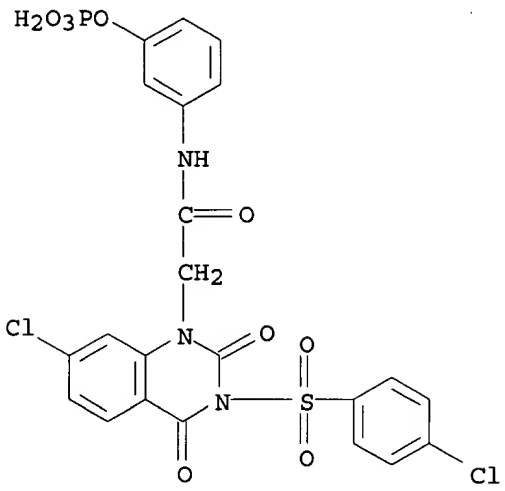
RN 189062-23-5 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3,4-dihydro-3-[(1-methyl-1H-pyrrol-3-yl)sulfonyl]-2,4-dioxo-N-3-pyridinyl- (9CI) (CA INDEX NAME)



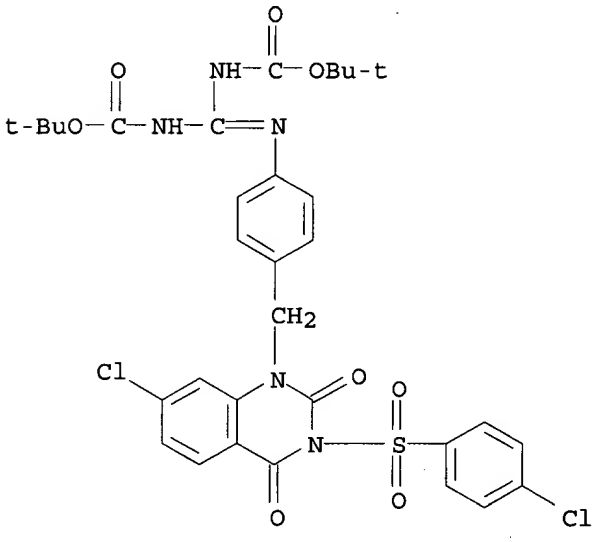
RN 189062-24-6 CAPLUS
CN 1H-Pyrazole-3-carboxylic acid, 5-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]-1-methyl-, ethyl ester (9CI) (CA INDEX NAME)



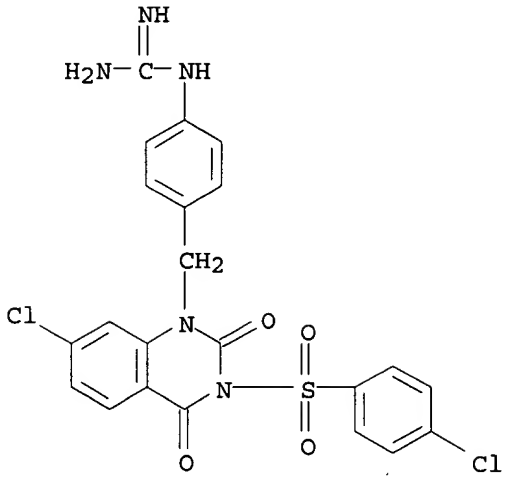
RN 189062-25-7 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-N-[3-(phosphonooxy)phenyl]- (9CI) (CA INDEX NAME)



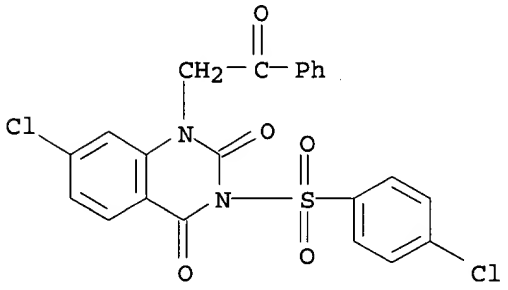
RN 189062-26-8 CAPLUS
CN Carbamic acid, [[4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]phenyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



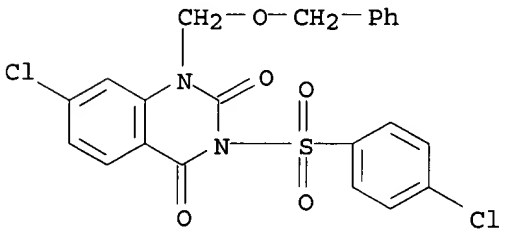
RN 189062-27-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 1-[[4-[(aminoiminomethyl)amino]phenyl]methyl]-7-chloro-3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



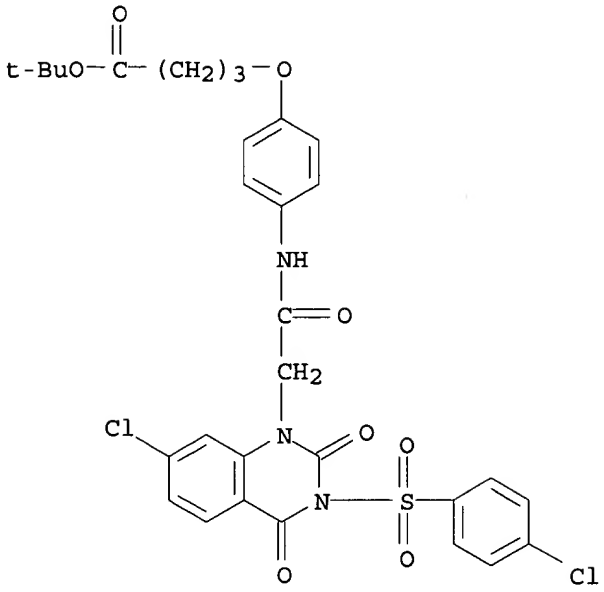
RN 189062-28-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(2-oxo-2-phenylethyl)- (9CI) (CA INDEX NAME)



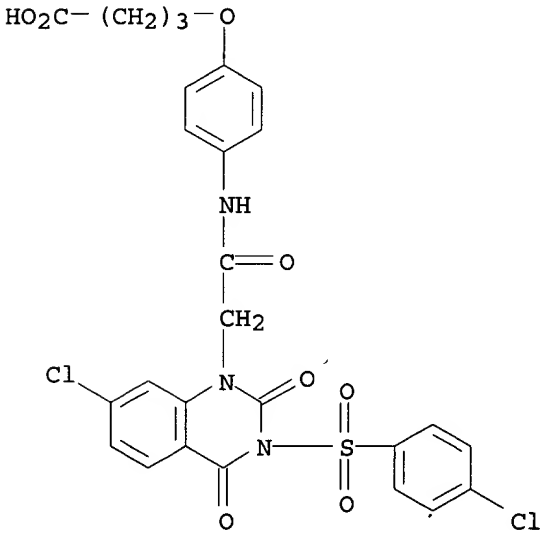
RN 189062-29-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-[(phenylmethoxy)methyl]- (9CI) (CA INDEX NAME)



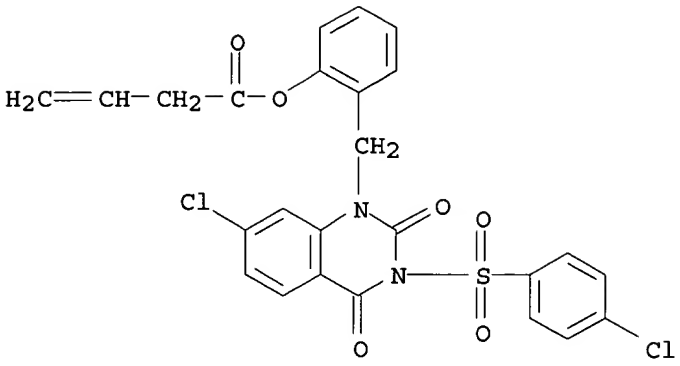
RN 189062-30-4 CAPLUS
CN Butanoic acid, 4-[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenoxy]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



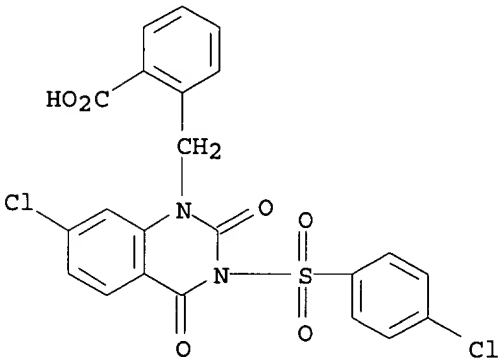
RN 189062-31-5 CAPLUS
CN Butanoic acid, 4-[4-[[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]acetyl]amino]phenoxy]- (9CI) (CA INDEX NAME)



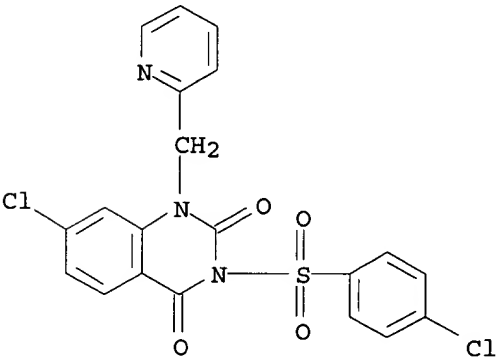
RN 189062-32-6 CAPLUS
CN 3-Butenoic acid, 2-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]phenyl ester (9CI) (CA INDEX NAME)



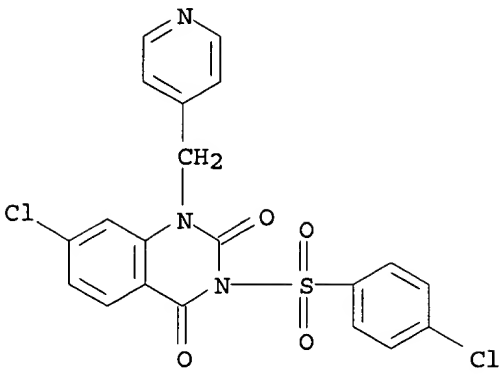
RN 189062-33-7 CAPLUS
CN Benzoic acid, 2-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]- (9CI) (CA INDEX NAME)



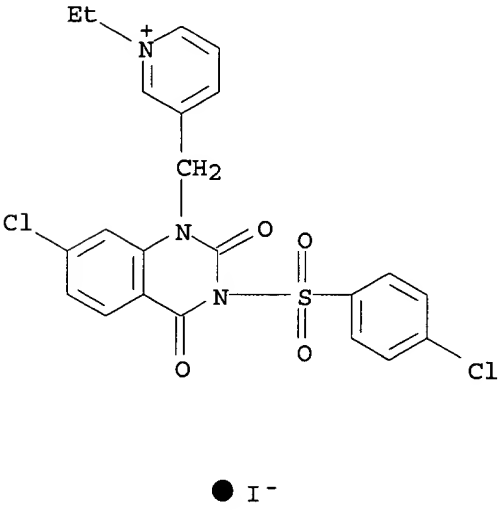
RN 189062-35-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(2-pyridinylmethyl)- (9CI) (CA INDEX NAME)



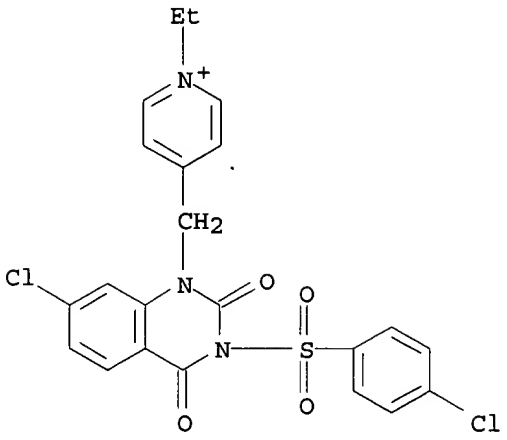
RN 189062-36-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)



RN 189062-37-1 CAPLUS
CN Pyridinium, 3-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-1-ethyl-, iodide (9CI) (CA INDEX NAME)

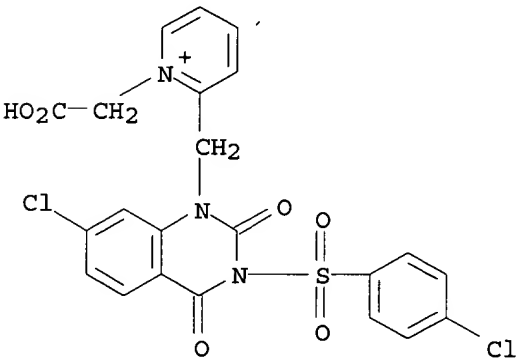


RN 189062-38-2 CAPLUS
CN Pyridinium, 4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-1-ethyl-, iodide (9CI) (CA INDEX NAME)



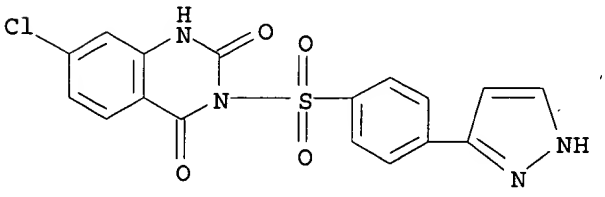
● I^-

RN 189062-39-3 CAPLUS
CN Pyridinium, 1-(carboxymethyl)-2-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-, bromide (9CI) (CA INDEX NAME)



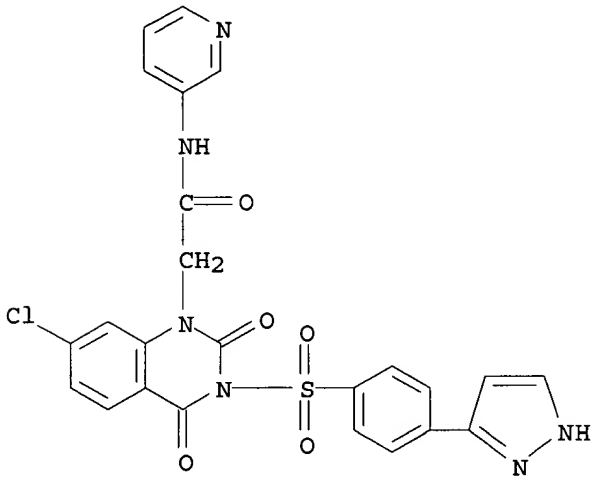
● Br^-

RN 189062-40-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)

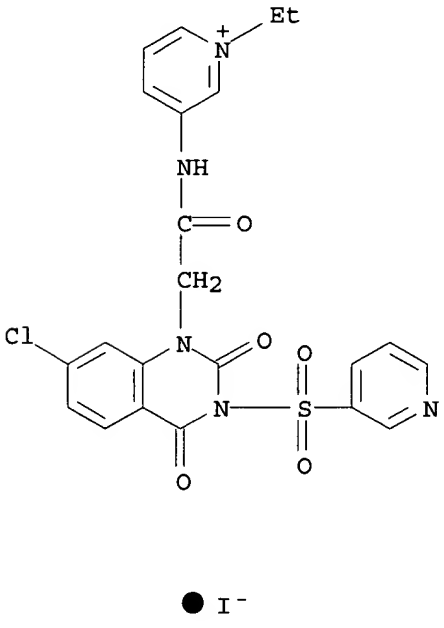


RN 189062-41-7 CAPLUS

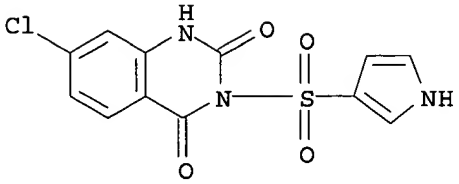
CN 1(2H)-Quinazolineacetamide, 7-chloro-3,4-dihydro-2,4-dioxo-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]-N-3-pyridinyl- (9CI) (CA INDEX NAME)



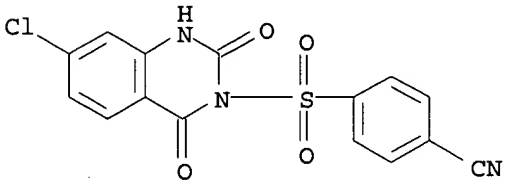
RN 189062-44-0 CAPLUS
CN Pyridinium, 3-[[[7-chloro-3,4-dihydro-2,4-dioxo-3-(3-pyridinylsulfonyl)-1(2H)-quinazolinyl]acetyl]amino]-1-ethyl-, iodide (9CI) (CA INDEX NAME)



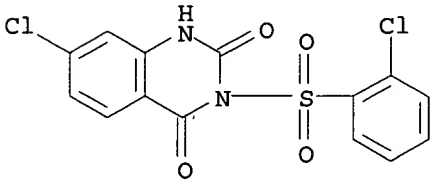
RN 189062-45-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-(1H-pyrrol-3-ylsulfonyl)- (9CI) (CA INDEX NAME)



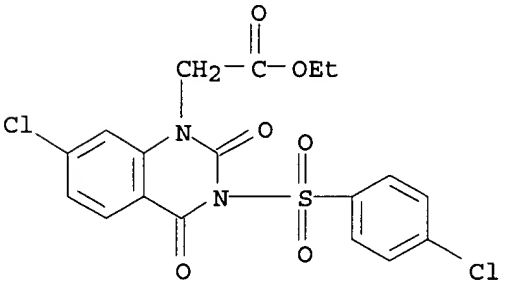
RN 189062-46-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-cyanophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



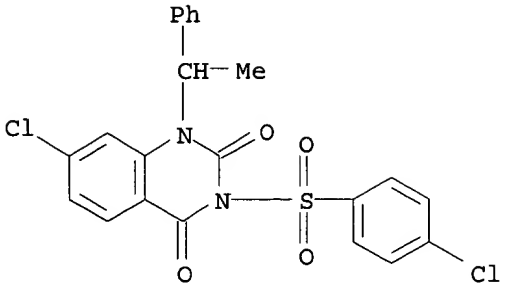
RN 189062-47-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



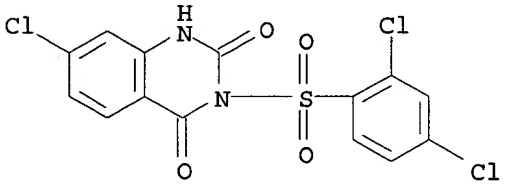
RN 189062-48-4 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



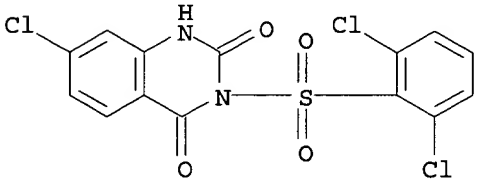
RN 189062-49-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-1-(1-phenylethyl)- (9CI) (CA INDEX NAME)



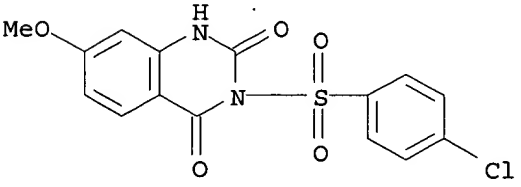
RN 189062-50-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2,4-dichlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



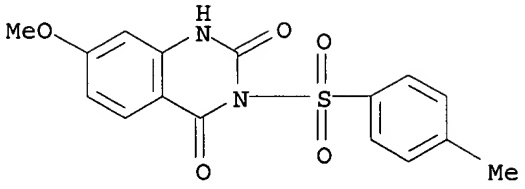
RN 189062-51-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2,6-dichlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



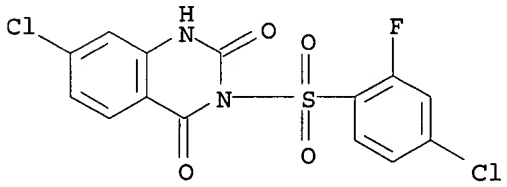
RN 189062-52-0 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-methoxy- (9CI) (CA INDEX NAME)



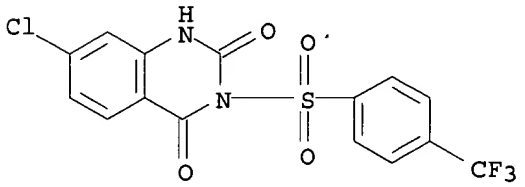
RN 189062-53-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-methoxy-3-[(4-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



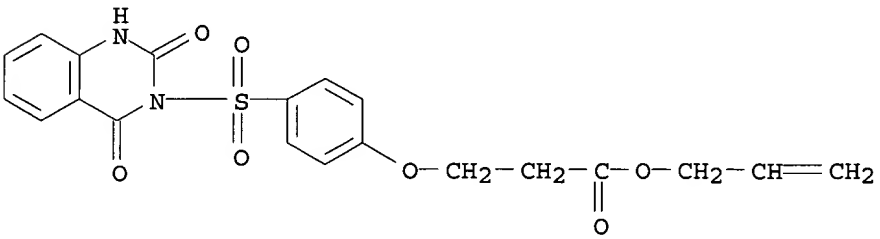
RN 189062-54-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chloro-2-fluorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



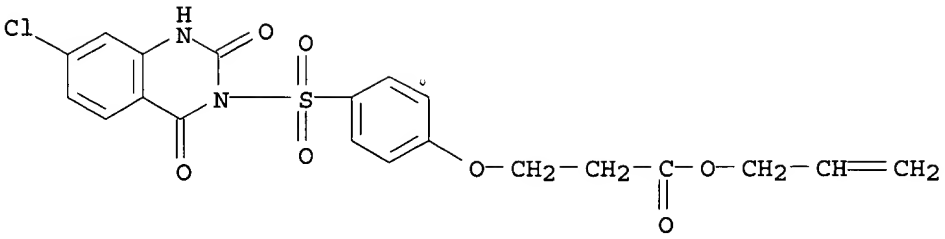
RN 189062-55-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(trifluoromethyl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



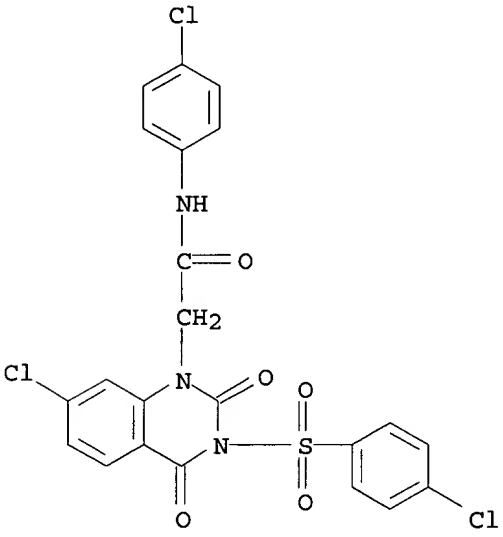
RN 189062-56-4 CAPLUS
CN Propanoic acid, 3-[4-[(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenoxy]-, 2-propenyl ester (9CI) (CA INDEX NAME)



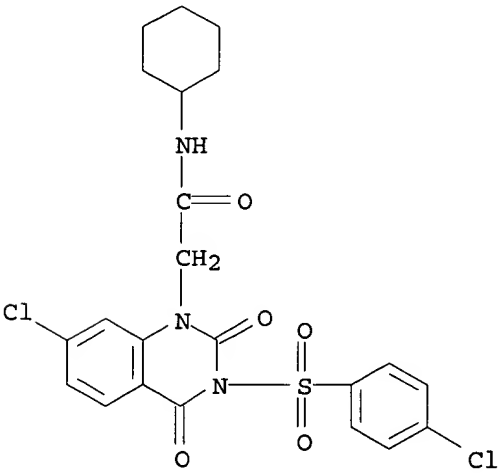
RN 189062-57-5 CAPLUS
CN Propanoic acid, 3-[4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenoxy]-, 2-propenyl ester (9CI) (CA INDEX NAME)



RN 189062-58-6 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-N-(4-chlorophenyl)-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)

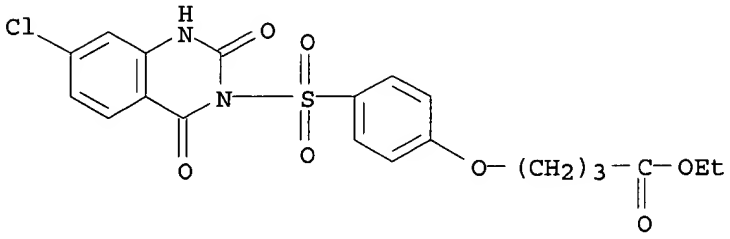


RN 189062-59-7 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-N-cyclohexyl-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)

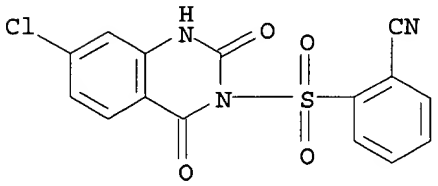


RN 189062-60-0 CAPLUS

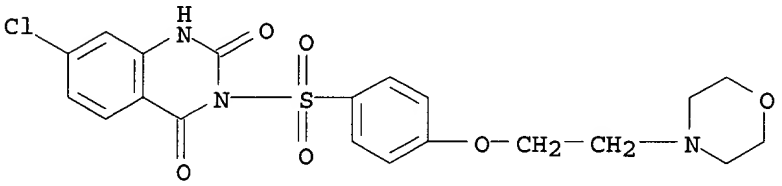
CN Butanoic acid, 4-[4-[(7-chloro-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)sulfonyl]phenoxy]-, ethyl ester (9CI) (CA INDEX NAME)



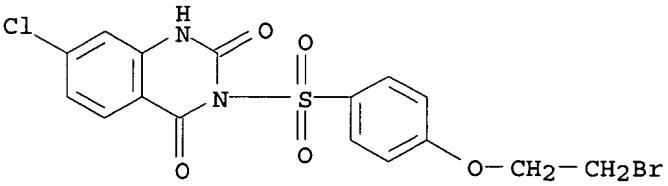
RN 189062-61-1 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(2-cyanophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



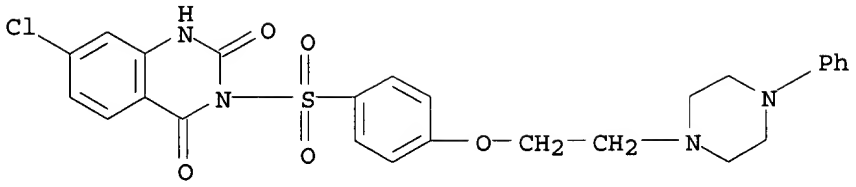
RN 189062-62-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-[2-(4-morpholinyl)ethoxy]phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



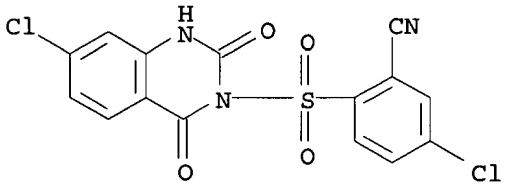
RN 189062-63-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[[4-(2-bromoethoxy)phenyl]sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



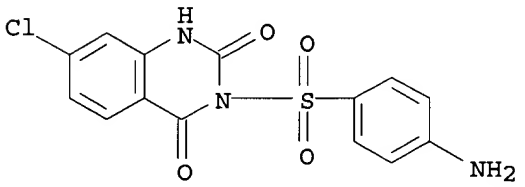
RN 189062-64-4 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-[2-(4-phenyl-1-piperazinyl)ethoxy]phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



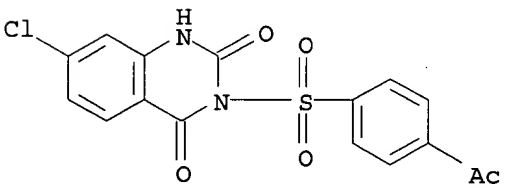
RN 189062-65-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[(4-chloro-2-cyanophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



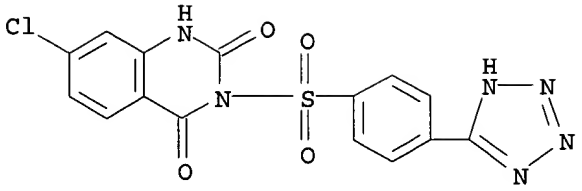
RN 189062-66-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-aminophenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



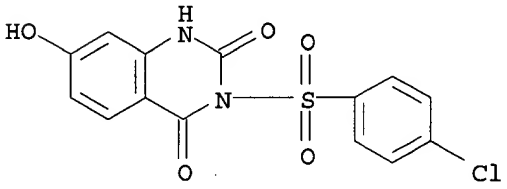
RN 189062-67-7 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-acetylphenyl)sulfonyl]-7-chloro- (9CI) (CA INDEX NAME)



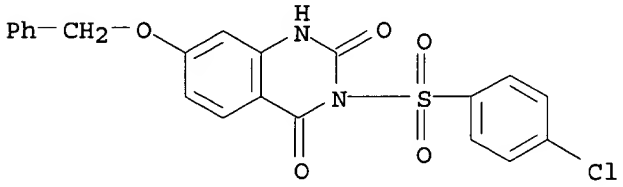
RN 189062-68-8 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 7-chloro-3-[[4-(1H-tetrazol-5-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 189062-69-9 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-hydroxy- (9CI) (CA INDEX NAME)

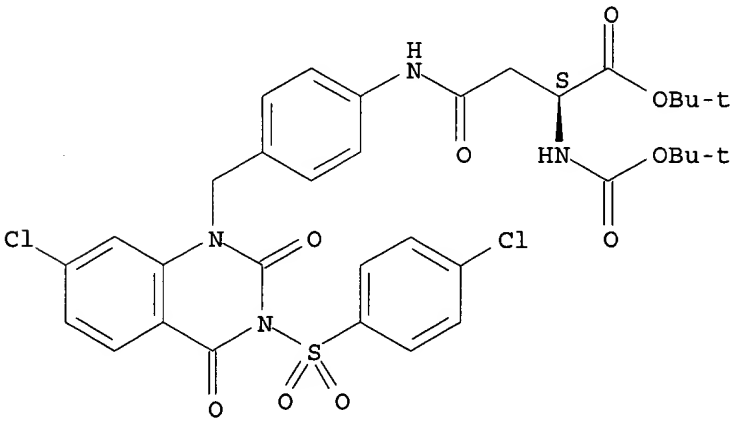


RN 189062-70-2 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]-7-(phenylmethoxy)- (9CI) (CA INDEX NAME)



RN 189062-73-5 CAPLUS
CN L-Asparagine, N-[4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]phenyl]-N2-[(1,1-dimethylethoxy)carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

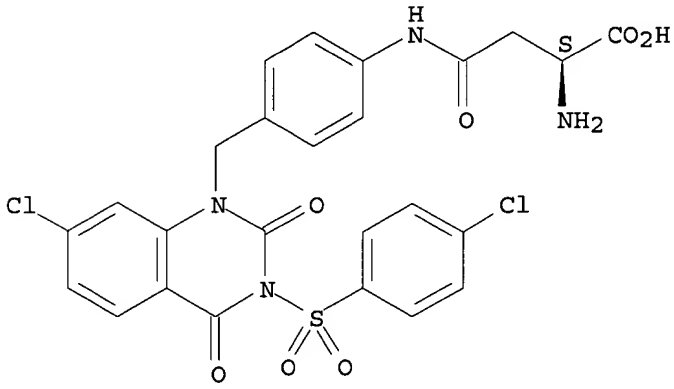
Absolute stereochemistry.



RN 189062-75-7 CAPLUS

CN L-Asparagine, N-[4-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]phenyl]- (9CI) (CA INDEX NAME)

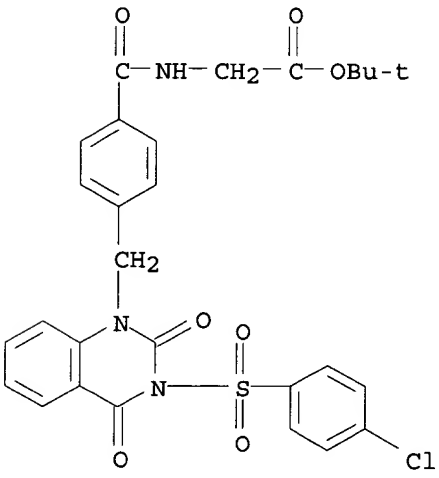
Absolute stereochemistry.



IT **189062-87-1P 189062-88-2P 189062-89-3P**
189062-91-7P 189062-92-8P 189062-93-9P
189062-94-0P 189062-95-1P 189062-96-2P
189062-97-3P 189063-02-3P 189063-03-4P
189063-06-7P 189063-11-4P 189063-16-9P
189063-17-0P 189063-19-2P 189063-20-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-phenylsulfonyl- and N-(heterocyclylsulfonyl)quinazoline derivs. as chymase inhibitors for treating heart or circulatory diseases)

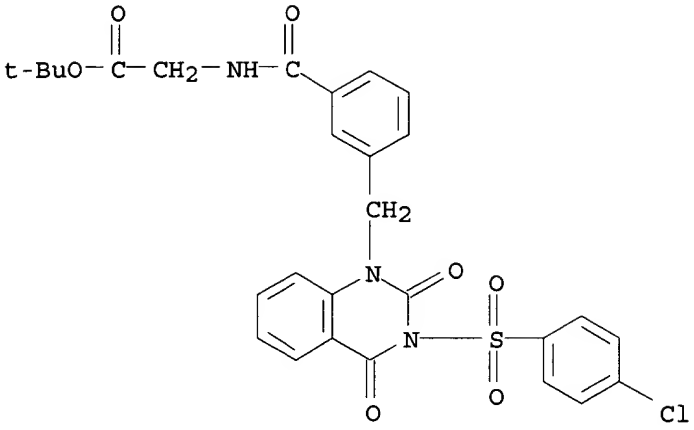
RN 189062-87-1 CAPLUS

CN Glycine, N-[4-[[3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]benzoyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

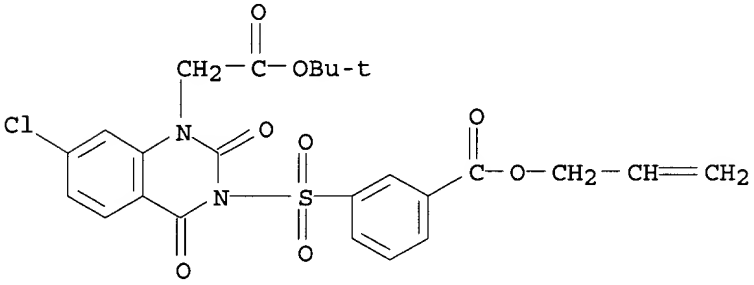


RN 189062-88-2 CAPLUS

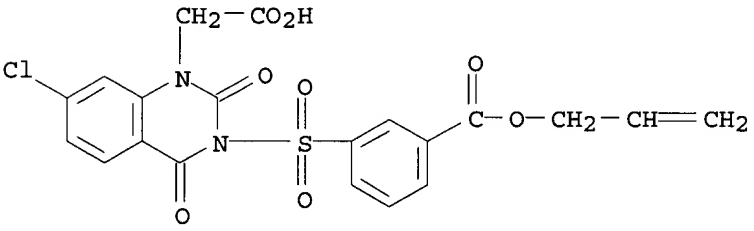
CN Glycine, N-[3-[[3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]benzoyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



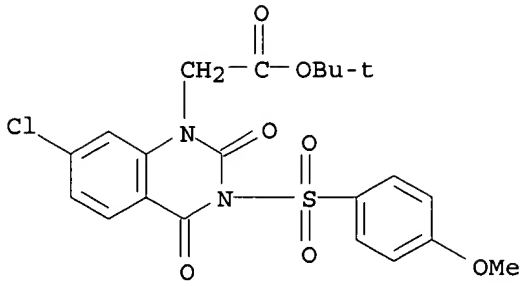
RN 189062-89-3 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-[[3-[(2-propenyloxy)carbonyl]phenyl]sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



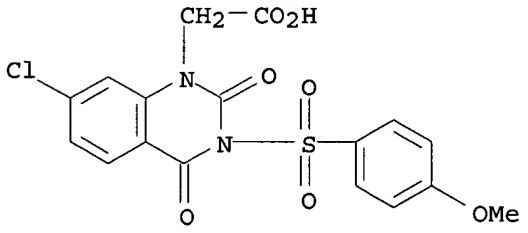
RN 189062-91-7 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-[[3-[(2-propenyloxy)carbonyl]phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



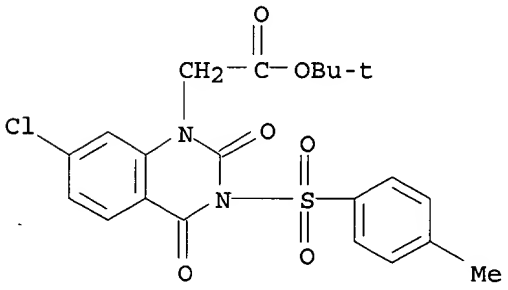
RN 189062-92-8 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-3-[(4-methoxyphenyl)sulfonyl]-2,4-dioxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



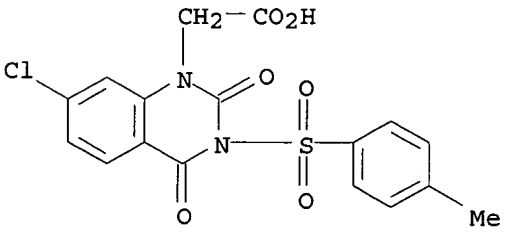
RN 189062-93-9 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-3-[(4-methoxyphenyl)sulfonyl]-2,4-dioxo- (9CI) (CA INDEX NAME)



RN 189062-94-0 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-3-[(4-methylphenyl)sulfonyl]-2,4-dioxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

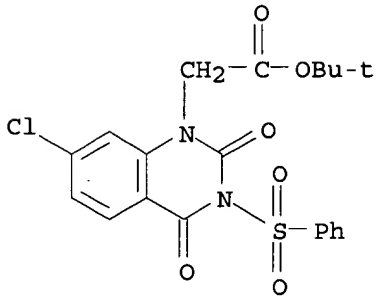


RN 189062-95-1 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-3-[(4-methylphenyl)sulfonyl]-2,4-dioxo- (9CI) (CA INDEX NAME)

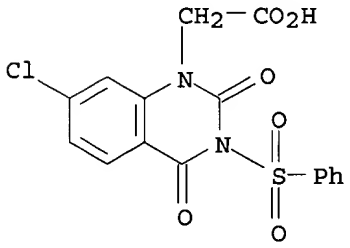


RN 189062-96-2 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-

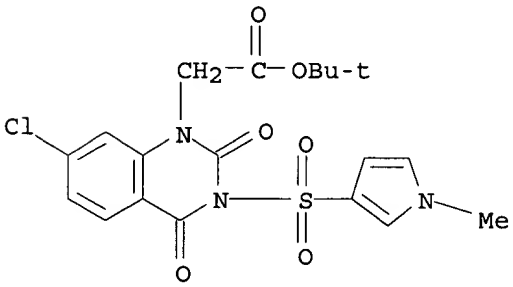
(phenylsulfonyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



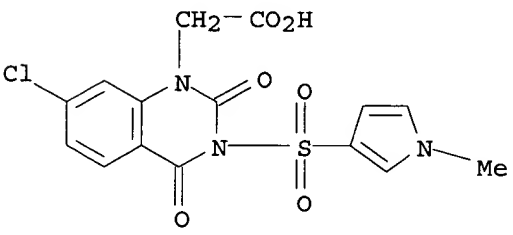
RN 189062-97-3 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



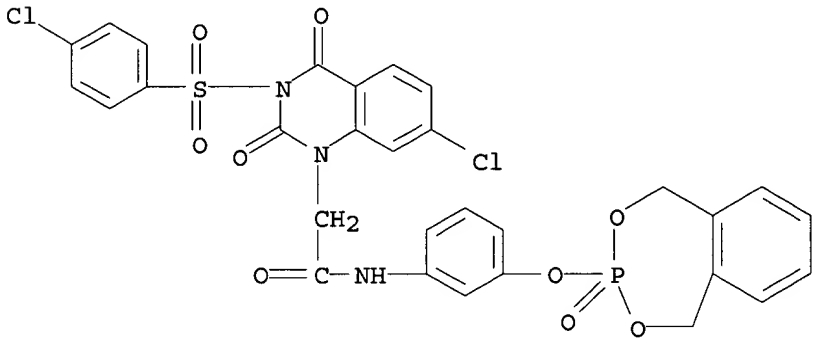
RN 189063-02-3 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-3-[(1-methyl-1H-pyrrol-3-yl)sulfonyl]-2,4-dioxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



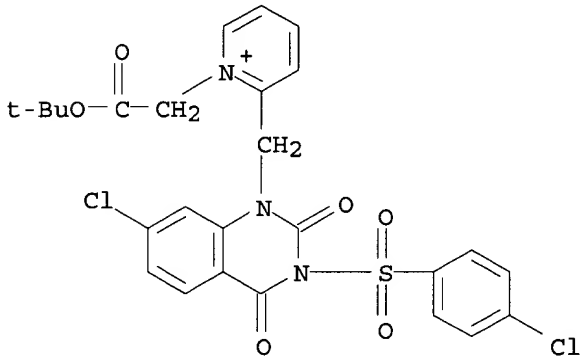
RN 189063-03-4 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-3-[(1-methyl-1H-pyrrol-3-yl)sulfonyl]-2,4-dioxo- (9CI) (CA INDEX NAME)



RN 189063-06-7 CAPLUS
CN 1(2H)-Quinazolineacetamide, 7-chloro-3-[(4-chlorophenyl)sulfonyl]-N-[3-[(1,5-dihydro-3-oxido-2,4,3-benzodioxaphosphepin-3-yl)oxy]phenyl]-3,4-dihydro-2,4-dioxo- (9CI) (CA INDEX NAME)

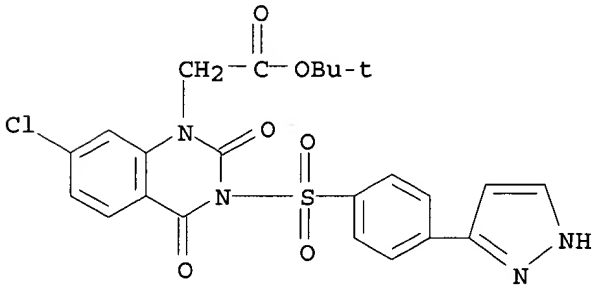


RN 189063-11-4 CAPLUS
CN Pyridinium, 2-[[7-chloro-3-[(4-chlorophenyl)sulfonyl]-3,4-dihydro-2,4-dioxo-1(2H)-quinazolinyl]methyl]-1-[2-(1,1-dimethylethoxy)-2-oxoethyl]-, bromide (9CI) (CA INDEX NAME)

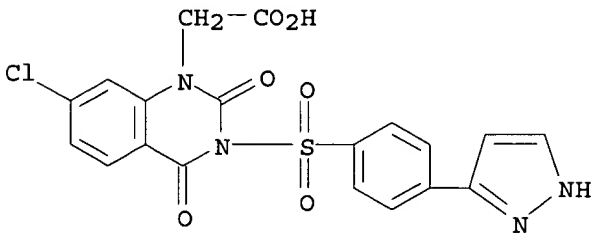


● Br^-

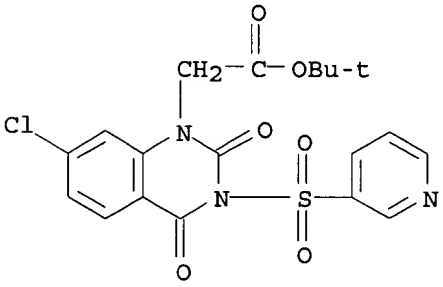
RN 189063-16-9 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



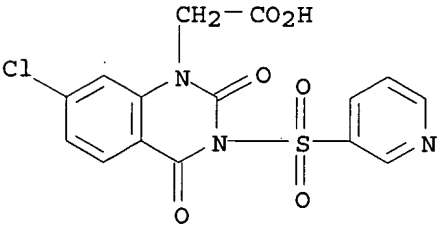
RN 189063-17-0 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-[[4-(1H-pyrazol-3-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 189063-19-2 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-(3-pyridinylsulfonyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 189063-20-5 CAPLUS
CN 1(2H)-Quinazolineacetic acid, 7-chloro-3,4-dihydro-2,4-dioxo-3-(3-pyridinylsulfonyl)- (9CI) (CA INDEX NAME)

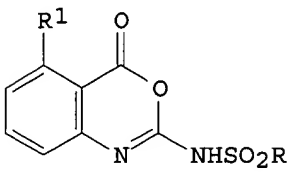


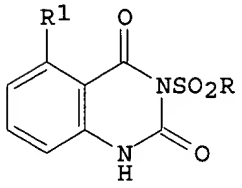
L11 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	1988:528941 CAPLUS
DOCUMENT NUMBER:	109:128941
TITLE:	Methyl N-(arylsulfonyl)dithiocarbamates as intermediates in heterocyclic synthesis. Preparation of the isomeric systems 2-arylsulfonylamino-3,1,4H-benzoxazin-4-ones and 3-arylsulfonyl-2,4-(1H,3H)-quinazolinediones
AUTHOR(S):	Garcia Tercero, J.; Lopez Aliaga, A.; Melendez Andreu, E.; Merchan Alvarez, F. L.; Tejero Lopez, T.
CORPORATE SOURCE:	Fac. Cienc., Univ. Zaragoza, Zaragoza, Spain
SOURCE:	An. Quim., Ser. C (1987), 83(2), 247-50 CODEN: AQSBD6; ISSN: 0211-1357
DOCUMENT TYPE:	Journal

09/ 869,360

LANGUAGE: Spanish
OTHER SOURCE(S): CASREACT 109:128941
GI

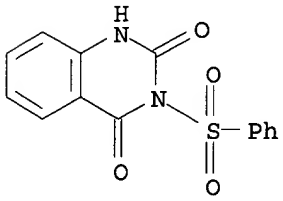

I


II

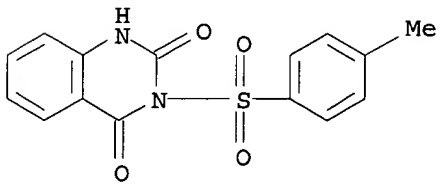
AB Treatment of K anthranilate or its 6-chloro deriv. with (arylsulfonyl)dithiocarbamates RSO2NHCS2Me (R = Ph, p-tolyl, p-ClC6H4), in the presence of HgO in DMF at room temp., afforded benzoxazinones I (R = Ph, R1 = H, Cl; R = p-tolyl, p-ClC6H4, R1 = H). When the reaction was carried out at higher temp. (50.degree. in THF), isomeric quinazolinediones II were obtained.

IT **116445-93-3P 116445-94-4P 116445-95-5P**
116445-96-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

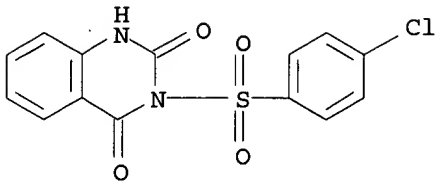
RN 116445-93-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



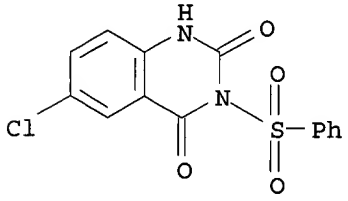
RN 116445-94-4 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 116445-95-5 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 3-[(4-chlorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 116445-96-6 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 6-chloro-3-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



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=> d his

     (FILE 'HOME' ENTERED AT 16:56:42 ON 02 SEP 2002)

     FILE 'REGISTRY' ENTERED AT 16:56:52 ON 02 SEP 2002
L1              STRUCTURE UPLOADED
L2           19 S L1
L3          218 S L1 FUL

     FILE 'CAPLUS' ENTERED AT 16:57:28 ON 02 SEP 2002
L4          385 S CHYMASE AND INHIBITOR?
L5      1203367 S VASCULAR OR LIPID OR BLOOD
L6        55122 S ARTERIOSCLEROSIS OR CORONARY OR ANGIOPLASTY OR CLAUDICATION
L7        59714 S (CEREBRAL INFARCTION) OR ANEURYSM OR GANGRENE OR HYPERTENSION
L8           51 S RENAL INFARCTION
L9      1249143 S L5 OR L6 OR L7 OR L8
L10         120 S L4 AND L9
L11           8 S L3

=> s l10 not l11
L12         117 L10 NOT L11

=> s l12 not py>1999
       2504924 PY>1999
L13          61 L12 NOT PY>1999

=> d l13 1- ibib abs
YOU HAVE REQUESTED DATA FROM 61 ANSWERS - CONTINUE? Y/(N):y

L13  ANSWER 1 OF 61  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2000:256284  CAPLUS
DOCUMENT NUMBER:          132:260073
TITLE:                    The place of angiotensin II antagonists in relation to
                          the canadian hypertension society guidelines
AUTHOR(S):                Carruthers, S. George
CORPORATE SOURCE:         London Health Sciences Centre, The University of
                          Western Ontario, London, ON, N6A 4G5, Can.
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09/ 869,360

SOURCE: Progress in Experimental Cardiology (1998), 2(Angiotensin II Receptor Blockade: Physiological and Clinical Implications), 93-103
CODEN: PEXCFF; ISSN: 1389-1774
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 19 refs. Angiotensin (Ang) II antagonists are a novel class of drugs developed to block Ang II receptors. This approach is deemed more direct and more likely to be effective than the earlier pharmacol. approach of inhibiting the enzyme (ACE **inhibitor**) responsible for converting Ang I to Ang II. Furthermore, it is expected that the approach will avoid problems assocd. with pathways that bypass ACE, e.g., tissue **chymase**. Two major subtypes of receptor have been identified, AT1 and AT2. Blockade of the AT1 receptor by a new class of agents typified by losartan lowers **blood** pressure in hypertensive subjects and has a theor. role in blocking the action of Ang II in the pathophysiol. of other disease states such as congestive heart failure (CHF) and left ventricular hypertrophy (LVH). The Canadian **Hypertension** Society Consensus Reports on the drug treatment of **hypertension** were last updated in a series of publications in the Canadian Medical Assocn. Journal in 1993. Specific reviews dealt with the pharmacotherapy of **hypertension**, the treatment of **hypertension** in the elderly, and the treatment of the diabetic hypertensive. The choice of antihypertensive therapy is driven by factors that include concurrent cardiovascular risk factors and the presence or absence of other disease states. The physician is challenged to find an appropriate medication for the individual patient that is not contraindicated, that is effective and affordable for the patient, and that does not cause adverse effects in managing this largely asymptomatic disorder. Although no long-term studies of AT1 blockers have been done in sufficiently large populations to det. the changes in clin. outcomes that are desirable in treating **hypertension** (e.g., redn. of myocardial infarction, stroke, and end-stage renal disease), the surrogate endpoint of **blood** pressure lowering indicates that AT1 blockers will have an important place in the management of **hypertension** that is akin to that presently held by ACE **inhibitors**, alpha-1 blockers, and calcium channel blockers. Recent evaluation of losartan in the elderly (ELITE) indicates a potentially valuable role for losartan in the treatment of elderly hypertensive patients with impaired left ventricular function.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:44837 CAPLUS
DOCUMENT NUMBER: 132:329222
TITLE: The renin-angiotensin-aldosterone system: A specific target for **hypertension** management
AUTHOR(S): Weir, Matthew R.; Dzau, Victor J.
CORPORATE SOURCE: Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: American Journal of Hypertension (1999), 12(12, Pt. 3), 205S-213S
CODEN: AJHYE6; ISSN: 0895-7061
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 69 refs. Angiotensin II plays a central role in the regulation of systemic arterial pressure through its systemic synthesis via the renin-angiotensin-aldosterone cascade. It acts directly on **vascular** smooth muscle as a potent vasoconstrictor. In addn., it affects cardiac contractility and heart rate through its action on the

sympathetic nervous system. Angiotensin II also alters renal sodium and water absorption through its ability to stimulate the zona glomerulosa cells of the adrenal cortex to synthesize and secrete aldosterone. Furthermore, it enhances thirst and stimulates the secretion of the antidiuretic hormone. Consequently, angiotensin II plays a crit. role in both the acute and chronic regulation of **blood** pressure through its systemic endocrine regulation. A potent neurohormone that regulates systemic arterial pressure, angiotensin II also affects **vascular** structure and function via paracrine and autocrine effects of local tissue-based synthesis. This alternate pathway of angiotensin II prodn. is catalyzed in tissues via enzymes such as cathepsin G, chymostatin-sensitive angiotensin II-generating enzyme, and **chymase**. Intratissue formation of angiotensin II plays a crit. role in cardiovascular remodeling. Upregulation of these alternate pathways may occur through stretch, stress, and turbulence within the **blood** vessel. Similar processes within the myocardium and glomeruli of the kidney may also lead to restructuring in these target organs, with consequent organ dysfunction. Addnl., angiotensin II may increase receptor d. and sensitivity for other factors that modulate growth of **vascular** smooth muscle, such as fibroblast growth factor, transforming growth factor .beta.-1, platelet-derived growth factor, and insulin-like growth factors. Atherosclerosis may also be related, in part, to excessive angiotensin II effect on the vessel wall, which causes smooth muscle cell growth and migration. It also activates macrophages and increases platelet aggregation. Angiotensin II stimulates plasminogen activator **inhibitor** 1 and directly causes endothelial dysfunction. Other postulated effects of angiotensin II on **vascular** structure that could promote atherogenesis include inhibition of apoptosis, increase in oxidative stress, promotion of leukocyte adhesion and migration, and stimulation of thrombosis. Inhibition of angiotensin II synthesis with an angiotensin-converting enzyme **inhibitor** has been demonstrated to be beneficial in modifying human disease progression. This is clearly apparent in clin. trials involving patients with diabetic nephropathy, postmyocardial infarction, or advanced degrees of systolic heart failure. Thus, angiotensin II is an excellent target for pharmacol. blockade. Not only does it play a pivotal role in both the acute and chronic regulation of systemic arterial pressure, but it also is an important modulator of cardiovascular structure and function and may be specifically involved in disease progression. Modification of angiotensin II effect may therefore serve a dual purpose. Not only will **blood** pressure redn. occur with less stretch, stress, and turbulence of the **vascular** wall, but there will also be less stimulation, either directly or indirectly, for restructuring and remodeling of the cardiovascular tree.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:44835 CAPLUS
DOCUMENT NUMBER: 132:329221
TITLE: Interrupting the renin-angiotensin system: The role of angiotensin-converting enzyme **inhibitors** and angiotensin II receptor antagonists in the treatment of **hypertension**
AUTHOR(S): Weber, Michael A.
CORPORATE SOURCE: Department of Medicine, The Brookdale University Hospital and Medical Center, Brooklyn, NY, 11212, USA
SOURCE: American Journal of Hypertension (1999), 12(12, Pt. 3), 189S-194S
CODEN: AJHYE6; ISSN: 0895-7061
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 33 refs. The renin-angiotensin system has two roles in clin. **hypertension**: its vasoconstrictor properties directly govern **blood** pressure, and its actions on arterial smooth muscle, connective tissue, and endothelial integrity affect cardiovascular prognosis. Addnl., the direct actions of angiotensin II on the function and structure of the heart and renal vasculature influence clin. events. Angiotensin-converting enzyme (ACE) **inhibitors** have produced functional and clin. outcome benefits in clin. trials of patients with congestive heart failure, systolic dysfunction after myocardial infarction, and diabetic nephropathy. Similar favorable trends have been noted in observational studies in **hypertension**. Because such enzymes as **chymase** can substitute for ACE, the ACE **inhibitors** may not completely block angiotensin II formation, although they enhance bradykinin accumulation and secondarily stimulate nitric oxide and vasodilatory prostaglandins. Angiotensin II receptor blockers (ARB) selectively block the angiotensin II type 1 (AT1) receptor that not only mediates the known effects of angiotensin II but, according to recent reports, might be responsible for sequestering angiotensin II mols. in renal and cardiac cells. Moreover, by increasing plasma concns. of angiotensin II, the ARB stimulate the unblocked angiotensin II type 2 (AT2) receptors, which - if they exist in meaningful nos. in human **hypertension** - mediate addnl. vasodilatory and antiproliferative effects. The contrasting actions of these two classes of drugs might be clin. relevant. For example, they may have additive antihypertensive efficacy; they have differing effects on renal plasma flow; and in a small pilot study of patients with congestive heart failure, the ARB demonstrated an apparent advantage in survival. Ongoing clin. trials will try to det. whether the effects of ARB can equal or even exceed the beneficial effects of ACE **inhibitors** on cardiovascular prognosis.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:29220 CAPLUS
DOCUMENT NUMBER: 132:288174
TITLE: Practical considerations of the pharmacology of angiotensin receptor blockers
AUTHOR(S): McConnaughey, Mona M.; McConnaughey, J. Scott; Ingenito, Alphonse J.
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, East Carolina University, Greenville, NC, 27858, USA
SOURCE: Journal of Clinical Pharmacology (1999), 39(6), 547-559
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 170 refs. A review of the drug class of angiotensin receptor blockers (ARBs) as well as the ARBs currently available by prescription in the United States is presented. The importance of angiotensin II prodn. by non-angiotensin-converting enzyme (non-ACE) pathways, particularly human **chymase**, is discussed. Emphasis is placed on the mechanism of action of ARBs and the different binding kinetics of these agents. Although all ARBs, as a group, block the AT1 receptor, they may differ in the pharmacol. characteristics of their binding and be classified as either surmountable or insurmountable antagonists. Mechanisms of surmountable and insurmountable antagonism as well as possible benefits of these blocking characteristics are discussed in relation to the various ARBs. The cardiovascular effects of activation of the two main subtypes of angiotensin receptors (AT1 and AT2) are presented. In addn. to their treatment of **hypertension**, ACE **inhibitors** are recognized as being effective in the management of

heart failure, left ventricular hypertrophy, recurrent myocardial infarctions, and renal disease. ARBs are currently indicated only for the treatment of **hypertension**; however, in vitro and in vivo pharmacol. studies as well as preliminary clin. data suggest that ARBs, like ACE **inhibitors**, may also provide effective protection against end-organ damage in these conditions.

REFERENCE COUNT: 170 THERE ARE 170 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:795994 CAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and

their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L13 ANSWER 6 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:686113 CAPLUS
DOCUMENT NUMBER: 132:31221
TITLE: Vasoconstriction by in situ formed angiotensin II: role of ACE and **chymase**
AUTHOR(S): MaassenVanDenBrink, A.; de Vries, R.; Saxena, P. R.; Schalekamp, M. A. D. H.; Danser, A. H. J.
CORPORATE SOURCE: Department of Pharmacology, Erasmus University, Rotterdam, 3015 GE, Neth.
SOURCE: Cardiovascular Research (1999), 44(2), 407-415
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies were carried out to assess the importance, for vasoconstriction, of in situ angiotensin (Ang) II generation, as opposed to Ang II delivery to AT receptors via the organ bath fluid. Ang I and II concn.-response curves in human and porcine **coronary** arteries (HCAs, PCAs) were constructed in relation to ests. of the clearances of Ang I and II (ClAngI, ClAngII) from the organ bath and the release of newly formed Ang II (RAngII) into the bath fluid. HCAs were from 25 heart valve donors (age 5-54 yr), and PCAs from 14 pigs (age 3 mo). Ang I- and II-evoked constrictions were inhibited by the AT1 receptor antagonist, irbesartan, and were not influenced by the AT2 receptor antagonist, PD123319. In HCAs Ang II was only three times more potent than Ang I, whereas, in the expts. with Ang I, comparison of ClAngI with ClAngII and RAngII indicated that most of the arterially produced Ang II did not reach the bath fluid. Also in PCAs Ang I and II showed similar potency. In HCAs both the ACE **inhibitor**, captopril, and the **chymase inhibitor**, chymostatin, inhibited Ang I-evoked vasoconstriction, while only chymostatin had a significant effect on ClAngI. In PCAs Ang I-evoked vasoconstriction was almost completely ACE-dependent. This study points towards the functional importance of in situ ACE- and **chymase**-dependent Ang II generation, as opposed to Ang II delivery via the circulation. It also indicates that functionally relevant changes in local Ang I-II conversion are not necessarily reflected by detectable changes in circulating Ang II.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:645934 CAPLUS
DOCUMENT NUMBER: 132:31211
TITLE: Alternative angiotensin II formation in rat arteries occurs only at very high concentrations of angiotensin

I

AUTHOR(S): Inoue, Kiyo; Nishimura, Hikaru; Kubota, Jiro; Kawamura, Keishiro

CORPORATE SOURCE: Third Department of Internal Medicine, Osaka Medical College, Osaka, 569-8686, Japan

SOURCE: Hypertension (1999), 34(3), 525-530
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Contrary to previous reports, recent enzymic assays showed the predominance of **chymase**-like activity in rat arteries. The authors detd. the existence and significance of such alternative pathways in rat carotid arteries by measuring contraction of arterial rings in organ baths and **blood** pressure in conscious rats. Hamster aorta served as a pos. control for **chymase**. Temocapril (30 .mu.M) inhibited the contractions to angiotensin (Ang) I (10-9 to 10-5 M) except at high concns. of Ang I (>10-7 M). Addn. of chymostatin (100 .mu.M) to temocapril exerted a synergistic **inhibitory** effect. Hamster aorta gave similar results, except that temocapril was 30-fold less effective than in rat arteries. [Pro11,D-Ala12]Ang I (10-8 to 10-5 M), a **chymase**-specific substrate, provoked similar responses in rat and hamster arteries; chymostatin, but not temocapril, attenuated the responses. CV 11974 (30 .mu.M), an Ang II type 1 receptor antagonist, abolished the responses to both peptides. In conscious rats, Ang I (0.03 to 30 .mu.g/kg) and [Pro11,D-Ala12]Ang I (7 to 700 .mu.g/kg) produced similar pressor responses. Not only CV 11974 (1 mg/kg) but also temocapril (2 mg/kg) abolished Ang I-induced responses in vivo. CV 11974, but not temocapril, inhibited responses to [Pro11,D-Ala12]Ang I. The authors' results showed the presence of the alternative pathway in rat arteries, but it did not play a major role. Arteries with the opposing characteristics of **chymase** responded equally to [Pro11,D-Ala12]Ang I. These findings suggest that biochem. and [Pro11,D-Ala12]Ang I-derived results may not reflect the functional significance of **chymase**.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:599338 CAPLUS
DOCUMENT NUMBER: 132:106848

TITLE: The effect of immediate-hypersensitivity reactions on the level of SLPI, granulocyte elastase, .alpha.1-antitrypsin, and albumin in nasal secretions, by the method of unilateral antigen challenge

AUTHOR(S): Westin, U.; Lundberg, E.; Wihl, J.-A.; Ohlsson, K.

CORPORATE SOURCE: Department of Otorhinolaryngology, University Hospital of Malmo, Malmo, Swed.

SOURCE: Allergy (Copenhagen) (1999), 54(8), 857-864
CODEN: LLRGDY; ISSN: 0105-4538
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The aim of this paper was to investigate the role of SLPI (secretory leukocyte protease **inhibitor**) in patients with allergic rhinitis. From this point of view, we also examd. leukocyte elastase, .alpha.1-antitrypsin, and albumin. SLPI is an **inhibitor** of serine proteases such as leukocyte elastase, cathepsin G, and mast-cell **chymase**. Since **chymase** is considered to participate in mast-cell degranulation and histamine release, SLPI might act as a regulator of allergic reactions. Recent interest has been focused on leukocytes and allergy. Since SLPI is a strong **inhibitor** of leukocyte elastase, we also focused on the function of elastase in

allergic rhinitis. Methods: We used the method of nasal lavage after unilateral nasal antigen challenge in atopic and healthy subjects. The ELISA quantified SLPI and elastase. Albumin and .alpha.1-antitrypsin were quantified by electroimmunoassay. Gel filtration was used to sep. native SLPI from its complex with elastase. Results: There was a higher level of SLPI in lavage fluid from healthy subjects than from atopic patients. SLPI was increased on the contralateral side in atopic subjects after allergen challenge. The absence of increase in SLPI on the challenged side may be attributed to the increase in elastase and its binding to SLPI, which might have an effect on the immunoreactivity and interfere with the ELISA. It may then be assumed that there is an augmentation of SLPI on the challenged side as well. No increase was seen in healthy subjects. There was a higher concn. of elastase, .alpha.1-antitrypsin, and albumin before antigen challenge in atopic patients outside the pollen season than in healthy subjects. As expected, an increase was also seen in the challenged side exclusively in atopic subjects. Conclusions: The lower concn. of SLPI in nasal lavage fluid among the atopic patients than the healthy subjects indicates damaged mucosa. Neural reflexes are involved in SLPI release since there was an increase even in the contralateral nostril. A higher level of elastase and albumin before allergen challenge suggests chronic inflammation in nasal mucosa outside the pollen season. Leukocyte recruitment takes place in response to IgE-mediated reactions, which are reflected in an increase in elastase in response to allergen challenge.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:578027 CAPLUS
DOCUMENT NUMBER: 131:347006
TITLE: **Chymase**-dependent angiotensin II formation in human **vascular** tissue
AUTHOR(S): Takai, Shinji; Jin, Denan; Sakaguchi, Masato; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan
SOURCE: Circulation (1999), 100(6), 654-658
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background-Some reports have suggested that, in vitro, human heart **chymase** in homogenates contributes little angiotensin (Ang) II formation in the presence of natural protease **inhibitors** such as .alpha.-antitrypsin. We studied whether **chymase** bound to heparin, resembling an in vivo form, could contribute to Ang II formation in the presence of natural protease **inhibitors**. Methods and Results-The Ang II formation was increased time-dependently after incubation in an ext. (1 mg protein/mL) of human **vascular** tissues contg. Ang I. The concn. of Ang II in the ext. after incubation 30 min was 1.67 nmol/mL, and we regarded this quantity of Ang II as 100%. The Ang II formation was inhibited 10%, 95%, and 96% by 1 .mu.mol/L lisinopril, 100 .mu.mol/L chymostatin, and 0.1 g/L .alpha.-antitrypsin, resp. The ext. was applied to a heparin affinity column. After the column was washed with PBS, the eluted PBS contain a weak Ang II-forming activity, which was completely inhibited by lisinopril. The eluted PBS, to which >0.8 mol/L NaCl had been added, showed a strong Ang II-forming activity which was inhibited by chymostatin and .alpha.-antitrypsin. After the application of the ext., the column was washed with PBS and then an Ang I soln. in PBS was applied to the column. The Ang II formation in the PBS eluted from the incubated column was increased time-dependently. The concn. of Ang II in the PBS (1 mL) eluted from the column after incubation for 30 min was 2.56 nmol/mL, and we regarded this quantity of

Ang II as 100%. To study the effects of **inhibitors**, the ext. (1 mg protein/mL) was applied to a heparin affinity column (1 mL) which was pre-equilibrated with PBS (3 mL); 100 .mu.mol/L chymostatin or 0.1 g/L .alpha.-antitrypsin in PBS (1 mL) was then applied to the column. After the column was washed with PBS (3 mL), Ang I soln. (1 mg/mL) in PBS was applied to the column, and the column was incubated for 30 min. The Ang II formation in the PBS eluted from the column was suppressed up to 5% by application of chymostatin although this was not affected by application of .alpha.-antitrypsin. Conclusions-These findings suggest that human **chymase** bound to heparin plays a functional role in Ang II formation in the presence of natural protease **inhibitors** such as .alpha.-antitrypsin.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:430947 CAPLUS
DOCUMENT NUMBER: 131:165658
TITLE: Mechanism of endothelin-1-(1-31)-induced calcium signaling in human **coronary** artery smooth muscle cells
AUTHOR(S): Inui, Daisuke; Yoshizumi, Masanori; Okishima, Naoko; Houchi, Hitoshi; Tsuchiya, Koichiro; Kido, Hiroshi; Tamaki, Toshiaki
CORPORATE SOURCE: Department of Pharmacology, The University of Tokushima School of Medicine, Tokushima, 770-8503, Japan
SOURCE: American Journal of Physiology (1999), 276(6, Pt. 1), E1067-E1072
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have found that human **chymase** produces a 31-amino acid endothelin [ET-1-(1-31)] from the 38-amino acid precursor (Big ET-1). The authors examd. the mechanism of synthetic ET-1-(1--31)-induced intracellular Ca2+ signaling in cultured human **coronary** artery smooth muscle cells. ET-1-(1--31) increased the intracellular free Ca2+ concn. ([Ca2+]i) in a concn.-dependent manner (10-14-10-10 M). This ET-1-(1-31)-induced [Ca2+]i increase was not affected by phosphoramidon, Bowman-Birk **inhibitor**, and thiorphan. The ET-1-(1-31)-induced [Ca2+]i increase was not influenced by removal of extracellular Ca2+ but was inhibited by thapsigargin. ET-1-(1-31) at 10-12 M did not cause Ca2+ influx, whereas 10-7 M ET-1-(1-31) evoked marked Ca2+ influx, which was inhibited by nifedipine. ET-1-(1-31) also increased inositol trisphosphate formation. These results suggest that the ET-1-(1-31)-induced [Ca2+]i increase at relatively low concns. is attributable to the release of Ca2+ from inositol trisphosphate-sensitive intracellular stores, whereas Ca2+ influx into the cells evoked by high concn. of ET-1-(1-31) probably occurs through voltage-dependent Ca2+ channels. The authors concluded that the physiol. activity of ET-1-(1-31) may be attributable to Ca2+ mobilization from intracellular stores rather than influx of Ca2+ from extracellular space.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:374593 CAPLUS
DOCUMENT NUMBER: 131:139920
TITLE: Evidence for angiotensin-converting enzyme- and **chymase**-mediated angiotensin II formation in the interstitial fluid space of the dog heart in vivo
AUTHOR(S): Wei, Chih-Chang; Meng, Qing C.; Palmer, Ronald;

Hageman, Gilbert R.; Durand, Joan; Bradley, Wayne E.; Farrell, Diane M.; Hankes, Gerald H.; Oparil, Suzanne; Dell'Italia, Louis J.
CORPORATE SOURCE: Birmingham Veteran Affairs Medical Center, Department of Medicine, Hypertension and Vascular Biology Program, Division of Cardiovascular Disease, Department of Physiology and Biophysics, University of Alabama at Birmingham, Auburn, AL, USA
SOURCE: Circulation (1999), 99(19), 2583-2589
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have previously demonstrated that angiotensin II (Ang II) levels in the interstitial fluid (ISF) space of the heart are higher than in the **blood** plasma and do not change after systemic infusion of Ang I. In this study, we assess the enzymic mechanisms (**chymase** vs. ACE) by which Ang II is generated in the ISF space of the dog heart in vivo. Cardiac microdialysis probes were implanted in the left ventricular (LV) myocardium (3 to 4 probes per dog) of 12 anesthetized open-chest normal dogs. ISF Ang I and II levels were measured at baseline and during ISF infusion of Ang I (15 .mu.mol/L), Ang I + the ACE **inhibitor** captopril (cap) (2.5 mmol/L), Ang I + the **chymase** **inhibitor** chymostatin (chy) (1 mmol/L), and Ang I + cap + chy. ISF infusion of Ang I increased ISF Ang II levels 100-fold, whereas aortic and **coronary** sinus plasma Ang I and II levels were unaffected and were 100-fold lower than ISF levels. Compared with ISF infusion of Ang I alone, Ang I + cap produced a greater redn. in ISF Ang II levels than did Ang I + chy (71% vs. 43%), whereas Ang I + cap + chy produced a 100% decrease in ISF Ang II levels. This study demonstrates for the first time a very high capacity for conversion of Ang I to Ang II mediated by both ACE and **chymase** in the ISF space of the dog heart in vivo.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:322204 CAPLUS
DOCUMENT NUMBER: 131:128475
TITLE: Differential Expression of Angiotensin-converting Enzyme and **Chymase** in Dogs with Chronic Mitral Regurgitation
AUTHOR(S): Su, Xuefeng; Wei, Chih-Chang; Machida, Naburo; Bishop, Sanford P.; Hankes, Gerald H.; Dillon, Ray A.; Oparil, Suzanne; Dell'Italia, Louis J.
CORPORATE SOURCE: Birmingham Veteran Affairs Medical Center, University of Alabama, Birmingham, AL, 35294, USA
SOURCE: Journal of Molecular and Cellular Cardiology (1999), 31(5), 1033-1045
CODEN: JMCDAY; ISSN: 0022-2828
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The current study tested the hypothesis that angiotensin-converting enzyme (ACE) and **chymase** expression are subject to different regulatory processes in the heart, as well as the lungs and kidneys and, as a result, have an important effect on the efficacy of ACE **inhibitor** treatment in modulating tissue angiotensin II (ANG II) levels in heart failure. A total of 18 dogs underwent the induction of mitral regurgitation and were followed for 5 mo. Eleven dogs were untreated and seven received the ACE-**inhibitor** ramipril at a dose of 10 mg PO BID. Seventeen dogs underwent a sham-operation: six of these dogs were treated with ramipril for 3 mo (10 mg PO BID) and 11 were untreated and followed for 3 mo prior to sacrifice. In mitral regurgitation dogs, ANG

II levels were increased >2-fold in left ventricle, lungs, and kidney, but were normalized with ACE **inhibitor**-treatment only in the left ventricle. In the left ventricle and lungs steady state ACE mRNA levels and ACE activities were increased 2-fold in treated and untreated mitral regurgitation dogs compared to shams ($P<0.05$, ANOVA). In contrast, **chymase** mRNA levels were decreased by >50% and **chymase** activity was increased in left ventricle (LV) of mitral regurgitation dogs ($P<0.05$). Neither **chymase** mRNA nor **chymase** activity could be detected in the kidney; however, kidney ACE mRNA and ACE activity were significantly upregulated in treated and untreated mitral regurgitation dogs ($P<0.05$). These results suggest that ACE and **chymase** expression are regulated differentially in the dog in response to chronic mitral regurgitation and ACE **inhibitor** treatment. Further, these responses, as well as regulation of ANG II formation, are organ specific. (c) 1999 Academic Press.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:180572 CAPLUS
DOCUMENT NUMBER: 131:27693
TITLE: Tranilast suppresses **vascular** **chymase** expression and neointima formation in balloon-injured dog carotid artery
AUTHOR(S): Shiota, Naotaka; Okunishi, Hideki; Takai, Shinji; Mikoshiba, Imao; Sakonjo, Hiroshi; Shibata, Nobuo; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki, 569, Japan
SOURCE: Circulation (1999), 99(8), 1084-1090
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of **vascular** **chymase** plays a major role in myointimal hypertrophy after **vascular** injury by augmenting the prodn. of angiotensin (ANG) II. Because **chymase** is synthesized mainly in mast cells, we assumed that the **chymase**-dependent ANG II formation could be downregulated by tranilast, a mast cell-stabilizing antiallergic agent. We have assessed **inhibitory** effects of tranilast on neointima formation after balloon injury in the carotid artery of dogs, which share a similar ANG II-forming **chymase** with humans, and further explored the pathophysiol. significance of **vascular** **chymase**. Either tranilast (50 mg/kg BID) or vehicle was orally administered to beagles for 2 wk before and 4 wk after balloon injury. Four weeks after the injury, remarkable neointima was formed in the carotid arteries of vehicle-treated dogs. **Chymase** mRNA levels and chymaselike activity of vehicle-treated injured arteries were increased 10.2- and 4.8-fold, resp., those of uninjured arteries. Angiotensin-converting enzyme (ACE) activity was slightly increased in the injured arteries, whereas ACE mRNA levels were not. Tranilast treatment completely prevented the increase in chymaselike activity, reduced the **chymase** mRNA levels by 43%, and decreased the carotid intima/media ratio by 63%. In vehicle-treated injured arteries, mast cell count in the adventitia showed a great increase, which was completely prevented by the tranilast treatment. **Vascular** ACE activity and mRNA levels were unaffected by tranilast. Tranilast suppressed **chymase** gene expression, which was specifically activated in the injured arteries, and prevented neointima formation. Suppression of the **chymase** -dependent ANG II-forming pathway may contribute to the beneficial effects of tranilast.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:159679 CAPLUS
DOCUMENT NUMBER: 130:309767
TITLE: Angiotensin II-forming systems in cardiovascular diseases
AUTHOR(S): Urata, Hidenori; Arakawa, Kikuo
CORPORATE SOURCE: Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, 814-80, Japan
SOURCE: Heart Failure Reviews (1998), 3(2), 119-124
CODEN: HFREFC; ISSN: 1382-4147
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 51 refs. Both the systemic and the tissue renin-angiotensin system (RAS)-are heavily involved in cardiovascular homeostasis, but their excess activation seems to be assocd. with increased morbidity and mortality in various stages of cardiovascular diseases, since angiotensin-converting enzyme (ACE) **inhibitors** have been shown to improve **hypertension**, congestive heart failure, and acute myocardial infarction. A clin. megastudy (ELITE) of elderly patients has recently shown that an AT1 receptor antagonist was superior to an ACE **inhibitor** for improvement of patients' prognosis. One of the possible mechanisms of this beneficial effect of the AT1 receptor antagonist compared to the ACE **inhibitor** could be the blockade of all the angiotensin (Ang) II formed not only by ACE but also by alternative pathways. Recent studies have disclosed that **chymase**, the most abundant Ang II-forming enzyme in human tissues, could be involved in the development of atherosclerosis, the remodeling of the myocardium after infarction or hypertrophy, restenosis after **vascular** injury, and chronic inflammatory conditions. Kallikrein-dependent Ang II formation also seems to take place under various ischemic conditions, as shown in the ischemic dog heart after ligation of a **coronary** artery, human leg circulation of patients with **arteriosclerosis** obliterans, or systemic circulation during a graded exercise. However, detailed mechanisms of non-ACE Ang II-forming enzymes involved in these pathol. changes are not known. Current knowledge about ACE and non-ACE Ang II-forming enzymes in cardiovascular diseases are reviewed in this article.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:118000 CAPLUS
DOCUMENT NUMBER: 130:332517
TITLE: Effect of an angiotensin II receptor antagonist, candesartan cilexetil, on canine intima hyperplasia after balloon injury
AUTHOR(S): Miyazaki, M.; Wada, T.; Shiota, N.; Takai, S.
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki-City, 569-8686, Japan
SOURCE: Journal of Human Hypertension (1999), 13(Suppl. 1), S21-S25
CODEN: JHHYEN; ISSN: 0950-9240
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The roles of angiotensin (Ang) II as produced by two different enzymes, angiotensin-converting enzyme (ACE) and **chymase**, were investigated in a canine exptl. model where intima hyperplasia was induced by balloon catheterization in the common carotid and femoral arteries. The animals received oral candesartan cilexetil (3 mg/kg) or enalapril (10 mg/kg) twice a day for 5 wk. After 1 wk of active drug therapy, the

common carotid and femoral arteries were unilaterally injured by balloon catheterization. In the common carotid arteries, both ACE and **chymase** activities were increased by the injury, with the increase in **chymase** activities being greater than that in ACE activities. In the femoral arteries, ACE, but not **chymase**, activities were significantly increased by the injury. Both candesartan cilexetil and enalapril reduced **blood** pressure almost equally. Enalapril increased plasma renin activity more strongly than did candesartan cilexetil, and significantly decreased **vascular** and plasma ACE activities. Candesartan cilexetil significantly suppressed the formation of intima hyperplasia in both the carotid and femoral arteries, while enalapril significantly suppressed intima hyperplasia in the femoral, but not in the carotid arteries. These results indicate that local Ang II prodn. by ACE and **chymase** is involved in the hyperplasia seen in injured intima, and the difference in the **inhibitory** action of candesartan and enalapril reflects the extent of contribution of each enzyme. The effect of the ACE **inhibitor**, enalapril, depended on the activity of ACE, whereas that of the Ang II receptor antagonist, candesartan, was independent of ACE activity.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:23267 CAPLUS
DOCUMENT NUMBER: 130:125063
TITLE: Preparation of hydrazide group-containing isoxazoles and their use as **inhibitors** of **chymase** and excess angiotensin II formation
INVENTOR(S): Ito, Kimio; Harada, Takeo; Hayashi, Yoshio; Muramatsu, Satoko; Katada, Jun
PATENT ASSIGNEE(S): Nippon Steel Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11001479	A2	19990106	JP 1997-154020	19970611

OTHER SOURCE(S): MARPAT 130:125063
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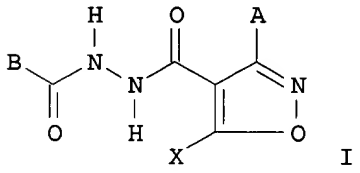


I

AB The title isoxazoles I [A, B = (un)substituted arom. hydrocarbyl; X = H, halo, alkyl], except 5-methyl-3-(2-chlorophenyl)-4-(3-chloro-4-fluorobenzoyl)hydrazinocarbonylisoxazole, are prepd. The isoxazoles are useful for treatment of **hypertension** and heart failure. Condensation of 3-chloro-4-fluorobenzoic acid hydrazide with 5-methyl-3-(2-chlorophenyl)-4-isoxazolecarbonyl chloride gave I (A = 2-ClC6H4, B = 3-chloro-4-fluorophenyl, X = Me), which inhibited human **chymase** with IC50 of 25 .mu.M.

L13 ANSWER 17 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:789462 CAPLUS
DOCUMENT NUMBER: 130:148101
TITLE: **Chymase**: Its pathophysiological roles and **inhibitors**
AUTHOR(S): Fukami, H.; Okunishi, H.; Miyazaki, M.
CORPORATE SOURCE: Research Center, Institute Biomedical Research, Shimamoto-cho, Mishima-gun, Osaka, 618, Japan
SOURCE: Current Pharmaceutical Design (1998), 4(6), 439-453
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 73 refs. **Chymase** is a chymotrypsin-type serine protease mainly localized in mast cells (MCs). Human primate, and dog **chymase** generate angiotensin II (Ang II) from Ang 1, while mouse and rat chymases degrade Ang II. It is suggested that **chymase** generating Ang II might be an alternative Ang II-forming enzyme to angiotensin-converting enzyme (ACE) in the renin-angiotensin system in tissues, but not in **blood**, and cause hypertrophy and remodeling of cardiovascular tissues. **Chymase** also degrades extracellular matrix, and processes procollagenase, inflammatory cytokines and other bioactive peptides. As a result, **chymase** plays important roles in inflammatory tissues through its proteolytic activities to cause tissue remodeling, i.e., a **chymase inhibitor** may have the ability to prevent diseases caused by the above inflammatory reactions. The investigation of **chymase inhibitors** by pharmaceutical companies has yielded peptide and peptide mimetic **inhibitors**. We also found potent non-peptide low mol. **inhibitors**. However, the in vivo functions of **chymase** have not been verified so far by applying a **chymase inhibitor** to in vivo pathol. models. In this article, we overview the pathophysiol. roles of **chymase** and **chymase inhibitors** proposed to date, and discuss the structure-activity relationships of substituted 3-phenylsulfonyl-1-phenylimidazolidine-2,4-dione derivs.
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 18 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:750453 CAPLUS
DOCUMENT NUMBER: 130:76578
TITLE: Dual pathway for angiotensin II formation in human internal mammary arteries
AUTHOR(S): Voors, Adriaan A.; Pinto, Yigal M.; Buikema, Hendrik; Urata, Hidenori; Oosterga, Margreeth; Rooks, Gerrit; Grandjean, Jan G.; Ganten, D.; Van Gilst, Wiek H.
CORPORATE SOURCE: Department of Clinical Pharmacology, University of Groningen, Groningen, 9713AV, Neth.
SOURCE: British Journal of Pharmacology (1998), 125(5), 1028-1032
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1 Angiotensin converting enzyme (ACE) is thought to be the main enzyme to convert angiotensin I to the vasoactive angiotensin II. Recently, in the human heart, it was found that the majority of angiotensin II formation was due to another enzyme, identified as human heart **chymase**. In the human vasculature however, the predominance of either ACE or non-ACE conversion of angiotensin I remains unclear. 2 To study the effects of ACE- and **chymase**-inhibition on angiotensin II formation in human arteries, segments of internal mammary arteries were

obtained from 37 patients who underwent **coronary** bypass surgery. 3 Organ bath expts. showed that 100 .mu.M captopril inhibited slightly the response to angiotensin I (pD2 from 7.09.+-.0.11-6.79.+-.0.10, P<0.001), while 100 .mu.M captopril nearly abolished the response to [pro10] angiotensin I, a selective substrate for ACE, and the max. contraction was reduced from 83.+-.19%-23.+-.17% of the control response (P=0.01). A significant decrease of the pD2 of angiotensin I similar to captopril was obsd. in the presence of 50 .mu.M chymostatin (pD2 from 7.36.+-.0.13-6.99.+-.0.15, P<0.039), without influencing the max. response. In the presence of both **inhibitors**, effects were much more pronounced than either **inhibitor** alone, and a 300 times higher dose was needed to yield a significant contraction response to angiotensin I. 4 These results indicate the presence of an ACE and a non-ACE angiotensin II forming pathway in human internal mammary arteries.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:750452 CAPLUS

DOCUMENT NUMBER: 130:76577

TITLE: Effect of endothelin-1 (1-31) on extracellular signal-regulated kinase and proliferation of human **coronary** artery smooth muscle cells

AUTHOR(S): Yoshizumi, Masanori; Kim, Shokei; Kagami, Shoji; Hamaguchi, Akinori; Tsuchiya, Koichiro; Houchi, Hitoshi; Iwao, Hiroshi; Kido, Hiroshi; Tamaki, Toshiaki

CORPORATE SOURCE: Department of Pharmacology, The University of Tokushima School of Medicine, Tokushima, 770-8503, Japan

SOURCE: British Journal of Pharmacology (1998), 125(5), 1019-1027
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1 We have previously found that human **chymase** cleaves big endothelins (ETs) at the Tyr31-Gly32 bond and produces 31-amino acid ETs (1-31), without any further degrdn. products. In this study, we investigated the effect of synthetic ET-1 (1-31) on the proliferation of cultured human **coronary** artery smooth muscle cells (HCASMCs). 2 ET-1 (1-31) increased [3H]-thymidine incorporation and cell nos. to a similar extent as ET-1 at 100 nM. This ET-1 (1-31)-induced [3H]-thymidine uptake was not affected by phosphoramidon, an **inhibitor** of ET-converting enzyme. It was, however, inhibited by BQ123, an endothelin ETA receptor antagonist, but not by BQ788, an endothelin ETB receptor antagonist. 3 By using an in-gel kinase assay, we demonstrated that ET-1 (1-31) activated extracellular signal-regulated kinase 1/2 (ERK1/2) in a concn.-dependent manner (100 pM to 1 .mu.M) in HCASMCs. ET-1 (1-31)-induced ERK1/2 activation was inhibited by BQ123, but not by BQ788 and phosphoramidon. Inhibition of protein kinase C (PKC) and ERK kinase also caused a redn. of ET-1 (1-31)-induced ERK1/2 activation, whereas tyrosine kinase inhibition had little effect. 4 Gel-mobility shift anal. revealed that the ERK1/2 activation was followed by an increase in transcription factor activator protein-1 DNA binding activity in HCASMCs. 5 Our results strongly suggest that ET-1 (1-31) itself stimulates HCASMC proliferation probably through endothelin ETA or ETA-like receptors. The underlining mechanism of cell growth by ET-1 (1-31) may be explained in part by PKC-dependent ERK1/2 activation. Since human **chymase** has been proposed to play a role in atherosclerosis, ET-1 (1-31) may be one of the mediators.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 20 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:725960 CAPLUS
DOCUMENT NUMBER: 130:61566
TITLE: Functional role of **chymase** in angiotensin II formation in human **vascular** tissue
AUTHOR(S): Takai, Shinji; Shiota, Naotaka; Jin, Denan; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, 5698686, Japan
SOURCE: Journal of Cardiovascular Pharmacology (1998), 32(5), 826-833
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent reports suggested that human heart **chymase** contributed little to angiotensin (Ang) II formation in the presence of natural protease **inhibitors** such as .alpha.-antitrypsin. We studied whether **chymase** could contribute to Ang II formation in the presence of natural protease **inhibitors** in the homogenate, the ext., and slices of human **vascular** tissue, and whether these **inhibitors** affect Ang I-induced vasocontractile responses due to **chymase**. In the homogenate, lisinopril, chymostatin, and .alpha.-antitrypsin inhibited the formation of Ang II by 14, 92, and 74%, resp. In the ext., the inhibition of Ang II formation by lisinopril, chymostatin, and .alpha.-antitrypsin was 18, 94, and 93%, resp. In the slices, lisinopril and chymostatin inhibited Ang II formation by 5 and 90%, resp. However, unlike the homogenate and the ext. expts., only 8% of the Ang II formation was suppressed by .alpha.-antitrypsin. In isolated human gastroepiploic artery, 30% of Ang I-induced vasoconstriction was blocked by lisinopril, and the rest was completely eliminated by a combination of lisinopril and chymostatin. On the other hand, .alpha.-antitrypsin was ineffective in blocking Ang I-induced vasoconstriction in the presence of lisinopril, which demonstrates that Ang II formation is dependent on **chymase**. These findings suggest that **chymase** in human **vascular** tissue plays a functional role in Ang II formation in the presence of natural protease **inhibitors** such as .alpha.-antitrypsin.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:689503 CAPLUS
DOCUMENT NUMBER: 130:20936
TITLE: Functional evidence for alternative ANG II-forming pathways in hamster cardiovascular system
AUTHOR(S): Nishimura, Hikaru; Buikema, Hendrik; Baltatu, Ovidiu; Ganten, Detlev; Urata, Hidenori
CORPORATE SOURCE: Max Delbrick Center for Molecular Medicine, Berlin, D-13122, Germany
SOURCE: American Journal of Physiology (1998), 275(4, Pt. 2), H1307-H1312
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Like human **chymase**, hamster **chymase** is an ANG II-forming enzyme, but pathophysiol. roles of **chymase** are still unknown. The authors detd. the functional conversion of ANG I and [Pro11, D-Ala12]ANG I, a **chymase**-selective substrate, to ANG II in the hamster cardiovascular system. ANG I and [Pro11, D-Ala-12]ANG I produced similar dose-dependent pressor responses in conscious hamsters. Captopril

and CV-11974, an ANG II type 1 (AT1)-receptor antagonist, inhibited the responses to ANG I; in contrast, the pressor responses to [Pro 11,D-Ala12]ANG I were suppressed only by CV-11974. In the isolated aorta, captopril suppressed ANG I-induced contraction by 84%; administration of captopril with either chymostatin or aprotinin eliminated the contraction. [Pro11, D-Ala12]ANG I-induced contraction was not affected by captopril but was attenuated by chymostatin (71%) and aprotinin (57%). CV-11974 abolished the responses to both substrates, whereas PD-123319, an AT2-receptor antagonist, had no effect. In homogenates of the aorta and heart, soybean trypsin **inhibitor**-inhibitable ANG II formation predominated over captopril- or aprotinin-inhibitable ANG II formation. These data suggest that [Pro11,D-Ala12]ANG I and part of ANG I were functionally converted to ANG II by **chymase** and other serine protease(s) in hamster vessels, inducing AT1-receptor-mediated vasoconstriction. Biochem. data supported a role for **chymase** in the alternative pathway.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 22 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:680934 CAPLUS
DOCUMENT NUMBER: 130:20951
TITLE: Alternative pathways of angiotensin II production in the human saphenous vein
AUTHOR(S): Borland, Julie A. A.; Chester, Adrian H.; Morrison, Karen A.; Yacoub, Magdi H.
CORPORATE SOURCE: Department of Cardiothoracic Surgery, National Heart and Lung Institute, Imperial College of Science Technology and Medicine, Heart Science Centre, Harefield Hospital, Uxbridge, UK
SOURCE: British Journal of Pharmacology (1998), 125(3), 423-428
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to demonstrate the existence, location and functional importance of an alternative angiotensin II-forming pathway other than angiotensin converting enzyme (ACE) in the human saphenous vein (SV). **Vascular** reactivity studies using an in vitro organ bath technique showed that the SV produced similar max. contractions in response to angiotensin I (41.5 mN) compared to those obsd. to angiotensin II (46.7 mN). The response to angiotensin I could be significantly inhibited by incubation with the AT1 receptor antagonist losartan (1 .mu.M). Prior incubation of segments of SV with either captopril (1 .mu.M), quinaprilat (1 .mu.M), or the **chymase inhibitor** soybean trypsin **inhibitor** (SBTI) (10 .mu.M) singularly failed to have any **inhibitory** effect on the response to angiotensin I. However when vessel segments were coincubated with quinaprilat (1 .mu.M) and SBTI (10 .mu.M), the SV exhibited a rightward shift in curve profile to angiotensin I and a markedly reduced max. response 12.5 mN, when compared to control (30.4 mN), quinaprilat (24.5 mN), and SBTI (31.6 mN) on their own. An immunohistochem. technique employing streptavidin biotin peroxidase localized ACE to both endothelial cells and smooth muscle cells while **chymase** was confined to mast cells in the adventitia of the vessel wall. In conclusion, the results demonstrate the existence of an alternative angiotensin I converting pathway to that of ACE, involving **chymase**. Therefore, there is the capacity for a continuation of angiotensin II formation. in the presence of ACE inhibition.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 23 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:576827 CAPLUS
DOCUMENT NUMBER: 129:214502
TITLE: Angiotensin II formation by **chymase** in the cardiovascular tissue
AUTHOR(S): Okunishi, Hideki
CORPORATE SOURCE: Dep. Pharmacol., Shimane Med. Univ., Izumo, 693-8501, Japan
SOURCE: Nippon Yakurigaku Zasshi (1998), 112(3), 203-212
CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 50 refs. Angiotensin-converting enzyme (ACE) **inhibitors** attenuated the contractile responses to angiotensin (Ang) I of arterial strips of humans, monkeys, and dogs, as can be expected. Unexpectedly, however, the response was not abolished by sufficient doses of ACE **inhibitors**, the facts suggesting the Ang I conversion by a non-ACE enzyme(s). HPLC anal. of the incubation product of Ang I with **vascular** tissues revealed that Ang II was yet formed despite complete ACE inhibition, and the ACE **inhibitor** -insensitive Ang II formation was blocked by chymostatin. The disclosed Ang II-forming enzyme was identified as **chymase**, which was later found in abundance in the human heart. Another notable discovery by us is the species difference in **chymase** processing of Ang I: chymases of the primates, dog, and hamster convert Ang I to Ang II, while chymases of rat, rabbit, and probably mouse do not. Accumulating evidence indicating that Ang II is not merely a vasopressor agent but also a growth-promoting factor, which leads to tissue hypertrophy and fibrosis, together with the results our studies lead us to propose the tissue-remodeling roles of **chymase** formed Ang II in various cardiovascular diseases: dog neointimal proliferation after **angioplasty**, hamster cardiomyopathy, etc., in which **chymase** mRNA is increased concordantly with tissue remodeling. The fact that Ang II receptor antagonists, not ACE **inhibitors**, suppress the tissue remodeling supports our argument that Ang II is formed predominantly by **chymase** in diseased tissues. Orally active **chymase inhibitors**, evolving in our study, should help explore the actual roles of **chymase** as well as the rational treatment of tissue-remodeling disorders.

L13 ANSWER 24 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:485632 CAPLUS
DOCUMENT NUMBER: 129:145180
TITLE: Human **chymase**, an enzyme forming novel bioactive 31-amino acid length endothelins
AUTHOR(S): Kido, Hiroshi; Nakano, Ayako; Okishima, Naoko; Wakabayashi, Hideki; Kishi, Fumiko; Nakaya, Yutaka; Yoshizumi, Masanori; Tamaki, Toshiaki
CORPORATE SOURCE: Division Enzyme Chemistry, Institute Enzyme Research, University Tokushima, Tokushima, 770, Japan
SOURCE: Biological Chemistry (1998), 379(7), 885-891
CODEN: BICHF3; ISSN: 1431-6730
PUBLISHER: Walter de Gruyter & Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors report the novel role of human **chymase** in the prodn. of bioactive 31-amino acid length endothelins (ETs), which may play a role in allergies and **vascular** diseases. In the bronchi of asthmatic patients, the **vascular** tissue in atherosclerosis, and the heart muscle in cardiac hypertrophy, both ET-like immunoreactivity and the accumulation of mast cells increase. **Chymase** from human mast cells selectively cleaves big ET-1, -2 and -3 at their Tyr31-Gly32 bonds, and produces novel bioactive 31-amino acid length ETs, ETs(1-31), without

any further degrdn. products. Chymases from other species, human cathepsin G, and porcine .alpha.-chymotrypsin, degrade big ETs. ETs(1-31) at concns. of 10-9-10-7 M exhibited various contractile potencies in rat tracheae and porcine **coronary** arteries in a dose-dependent manner. ET-1(1-31) at concns. of 10-14-10-10 M caused an increase in the intracellular free Ca2+ concn. The contractile activity of ETs(1-31) may not be the consequence of conversion to the corresponding ETs(1-21) by phosphoramidon-sensitive ET converting enzyme(s) or other chymotrypsin-type proteases and metallo-endopeptidases, because the contractile activity was not inhibited on treatment with **inhibitors** of these proteases prior to the addn. of ET-1(1-31).

L13 ANSWER 25 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:448932 CAPLUS
DOCUMENT NUMBER: 129:202044
TITLE: The induction of a prolonged increase in microvascular permeability by human mast cell **chymase**
AUTHOR(S): He, Shaoheng; Walls, Andrew F.
CORPORATE SOURCE: Immunopharmacology Group, Southampton General Hospital, Southampton, SO16 6YD, UK
SOURCE: European Journal of Pharmacology (1998), 352(1), 91-98
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Chymase** is a major constituent of the secretory granules of human mast cells, but little is known of the contribution of this serine proteinase in acute allergic reactions. The authors have purified **chymase** from human skin tissue, and have investigated its potential to induce microvascular leakage in vivo. Injection of **chymase** into the skin of guinea pigs provoked an increase in microvascular leakage within 20 min. Although skin reactions were smaller than those elicited with similar quantities of histamine at this time point, they were much longer-lived, and were still apparent 120 min following injection. **Chymase** induced microvascular leakage was reduced in the presence of soybean trypsin **inhibitor**, and abolished by heat inactivating the enzyme, indicating dependence on an intact catalytic site. Little evidence was found for synergistic interactions between **chymase** and either histamine or tryptase. Antihistamine pretreatment of animals did not reduce the magnitude of skin reactions to **chymase** suggesting that they were not mediated by histamine release. **Chymase** could contribute to increases in microvascular permeability following mast cell degranulation in allergic disease.

L13 ANSWER 26 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:383678 CAPLUS
DOCUMENT NUMBER: 129:160084
TITLE: Roles of **vascular** angiotensin converting enzyme and **chymase** in two-kidney, one clip hypertensive hamsters
AUTHOR(S): Jin, Denan; Takai, Shinji; Shiota, Naotaka; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki, 569, Japan
SOURCE: Journal of Hypertension (1998), 16(5), 657-664
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A **chymase**-dependent angiotensin II-forming pathway is present in human **vascular** tissues; however, the role, if it plays any, of **chymase** in the pathogenesis of **hypertension** is not

known. When investigating the role of **chymase**, it is important to recognize marked differences in **vascular** angiotensin II-forming systems among species. The authors found recently that hamsters, like humans, possess the dual angiotensin II-forming system. To analyze the potential involvement of angiotensin-converting enzyme and **chymase** in the pathogenesis of **hypertension**, and to further characterize the efficiency of angiotensin-converting enzyme **inhibitors** and angiotensin II receptor antagonists for the treatment of **hypertension**. The mean arterial pressure in the two-kidney, one clip hamster model had increased 2 wk after clipping (acute stage), reached a peak after 4 wk, and was sustained at the high level until 32 wk after clipping (chronic stage). Plasma renin activity increased markedly during the acute stage, but returned to the normal level during the chronic stage. **Vascular** angiotensin-converting enzyme activity during 4-32 wk after clipping was higher than that in the control hamsters. By contrast, **vascular chymase** was not activated throughout the exptl. period. Administrations of an angiotensin-converting enzyme **inhibitor**, trandolapril, and an angiotensin II receptor antagonist, CV-11974, equally lowered the mean arterial pressure during the acute and chronic stages. **Vascular** angiotensin-converting enzyme plays a predominant role in the maintenance of two-kidney, one clip **hypertension** in hamsters, which, like humans, possess a dual system of formation of angiotensin II. **Vascular chymase** was not involved in the pathogenesis of two-kidney, one clip **hypertension** in the hamster.

L13 ANSWER 27 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:306043 CAPLUS
DOCUMENT NUMBER: 129:76944
TITLE: Endothelin-1-(1-31), a novel vasoactive peptide, increases [Ca2+]i in human **coronary** artery smooth muscle cells
AUTHOR(S): Yoshizumi, Masanori; Inui, Daisuke; Okishima, Naoko; Houchi, Hitoshi; Tsuchiya, Koichiro; Wakabayashi, Hideki; Kido, Hiroshi; Tamaki, Toshiaki
CORPORATE SOURCE: Department of Pharmacology, The University of Tokushima School of Medicine, Tokushima, 770-8503, Japan
SOURCE: European Journal of Pharmacology (1998), 348(2/3), 305-309
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously found that human **chymase** cleaves big endothelins at the Tyr31-Gly32 bond and produces 31-amino acid long endothelins-(1-31), without any further degrdn. products. In this study, the authors investigated the effect of synthetic endothelin-1-(1-31) on the intracellular free Ca2+ concn. ([Ca2+]i) in cultured human **coronary** artery smooth muscle cells. Endothelin-1-(1-31) increased [Ca2+]i in a concn.-dependent manner (10-14 to 10-10 M). This endothelin-1-(1-31)-induced [Ca2+]i increase was not affected by phosphoramidon (N-(.alpha.-Rhamnopyranosyloxyhydroxyphosphinyl)-l-Leucyl-l-Tryptophan), an **inhibitor** of endothelin-converting enzyme. It was, however, inhibited by 10-10 M BQ123 (Cyclo-(-d-Trp-d-Asp(ONa)-Pro-d-Val-Leu-)), an endothelin ETA receptor antagonist, but not by 10-10 M BQ788 (N-cis-2,6-dimethylpiperidinocarbonyl-l-.gamma.MeLeu-d-Trp(COOMe)-d-Nle-ONa), an endothelin ETB receptor antagonist. These results suggest that endothelin-1-(1-31) by itself exhibits vasoactive properties probably through endothelin ETA receptors. Since human **chymase** has been reported to play a role in atherosclerosis, endothelin-1-(1-31) may be one of the candidate substances for its cause.

L13 ANSWER 28 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:288415 CAPLUS
DOCUMENT NUMBER: 128:290021
TITLE: **Inhibitory** effects of tranilast on neointima formation in canine balloon-injured carotid arteries: pathophysiological functions of **chymase** -dependent angiotensin II
AUTHOR(S): Mikoshiba, Imao
CORPORATE SOURCE: Dep. Pharmacology, Osaka Med. College, Takatsuki, Japan
SOURCE: Osaka Ika Daigaku Zasshi (1997), 56(3), 62-74
CODEN: OIDZAU; ISSN: 0030-6118
PUBLISHER: Osaka Ika Daigaku Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB In addn. to the angiotensin converting enzyme (ACE)-dependent pathway, the **chymase**-dependent angiotensin (Ang)II-forming pathway plays a major role in myointimal proliferation following **vascular** injury, and the involvement of **chymase** is of interest in the mechanisms of restenosis after percutaneous transluminal **coronary angioplasty** (PTCA) in humans. Since **chymase** is primarily produced in mast cells and secreted into the interstitium, there is a possibility that the **chymase**-dependent Ang II-forming pathway may be inhibited by anti-allergic agents that suppress activation of mast cells. In the present study, we assessed the **inhibitory** effects of an anti-allergic agent, tranilast, on intimal thickening following balloon injury in the canine carotid artery, and we further investigated the possible roles of **chymase** and ACE, the two major **vascular** AngII-forming enzymes, in the pathogenesis of neointima formation. Five beagle dogs were treated with tranilast (50 mg/kg, twice daily, p. o.) and seven with placebo. After a two-week treatment period, a balloon catheter was inserted into the right common carotid artery to induce intimal injury, while the left common carotid artery was kept intact and used as an uninjured control. Following intimal injury, the dogs were treated with tranilast or placebo for another four weeks. Then, the animals were killed, and the injured and uninjured arteries were excised for pathol. anal. and measurement of **chymase**-like activity, ACE activity, and their mRNA levels. In the placebo group, marked intimal thickening was seen as a result of neointima formation in the injured arteries, and numerous mast cells appeared in adventitia. **Vascular chymase**-like activities and **chymase** mRNA levels in the injured arteries were 10.2-fold and 4.8-fold, resp., compared with those of the uninjured arteries were 10.2-fold and 4.8-fold, resp., compared with those of the uninjured arteries. **Vascular** ACE activities were slightly increased in the injured arteries, while **vascular** ACE mRNA levels did not differ between injured and uninjured arteries. In the tranilast-treated group, neointima formation was significantly suppressed in the injured arteries, and the no. of adventitial mast cells was significantly decreased. **Vascular chymase**-like activities in the injured arteries were completely suppressed, and **chymase** mRNA levels were reduced by 56.7%. However, **vascular** ACE activities and mRNA levels were not affected by chronic treatment with tranilast. These results demonstrate that **chymase**-dependent Ang II plays a more important role in intimal thickening in balloon-injured arteries than ACE-dependent Ang II. Tranilast is effective for the prevention of neointima formation following balloon injury, and inhibition of the **chymase**-dependent Ang II-forming pathway is implicated in the mechanisms of this action.

L13 ANSWER 29 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:149790 CAPLUS
DOCUMENT NUMBER: 128:203726

09/ 869,360

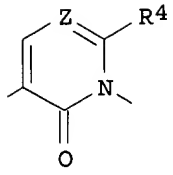
TITLE: Role of tissue angiotensin II production system in **hypertension** and atherosclerosis
AUTHOR(S): Ogiwara, Toshio; Higaki, Jitsuo; Rakugi, Hiromi; Moriguchi, Atsushi
CORPORATE SOURCE: Med. Sch., Osaka Univ., Suita, 565, Japan
SOURCE: Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku (1997), Volume Date 1996, 15, 188-192
CODEN: IOKHEP; ISSN: 0914-5117
PUBLISHER: Ikagaku Oyo Kenkyu Zaidan
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

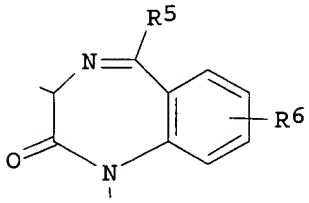
AB Angiotensin converting enzyme (ACE) was expressed in concordance with the active period of epithelial proliferation in atherosclerosis in human. Forced expression of ACE gene in rat procelia resulted elevation of **blood** pressure. ACE was detected in the smooth muscle cells of fibrous cap and macrophage in fibro-**lipid** plaque, and was not detected in the subintimal region of fibrosclerotic plaque in human **coronary** artery tissue. Normal human **coronary** artery tissue expressed ACE only in epithelial cells. The localization of angiotensin II was almost in concordance with the expression regions of ACE. **Chymase** was expressed mainly around **blood** vessel and only in penetrating g mast cells in subintimal region. Forced expression of human ACE in rat procelia increased brain angiotensin II concn. from 7.5 .+-. 0.3 pg/g to 11.1 .+-. 0.4 pg/g, which resulted the increment of the **blood** pressure from 127 .+-. 5 mm HG to 150.4 .+-. 4 mmHg at day 5 after the expression. The pulse no. increased with similar fashion to **blood** pressure. Administration of delapril, an ACE **inhibitor**, decreased the **blood** pressure in the ACE-introduced rat when the drug was administered into procelia. Peripheral administration of delapril was ineffective.

L13 ANSWER 30 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:126655 CAPLUS
DOCUMENT NUMBER: 128:192666
TITLE: Preparation of acetamides, their use as **chymase inhibitors** and angiotensin II **inhibitors**, and cardiovascular agents containing them
INVENTOR(S): Akaha, Atsushi; Takenaka, Kohei; Itani, Hiromichi; Sato, Akihiro; Nakanishi, Isao
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10053579	A2	19980224	JP 1997-160803	19970618

PRIORITY APPLN. INFO.: AU 1996-626 19960624
OTHER SOURCE(S): MARPAT 128:192666
GI

Q1 = 

Q2 = 

AB R1NHXYCONHCHR2COR3 I [R1 = H, protecting group; R2 = ar(lower)alkyl; R3 = lower haloalkyl, (protected) CO2H; X = Q1, Q2; R4, R5 = halo-, lower alkoxy-, or Ph-substituted aryl, cyclo(lower)alkyl; R6 = H, lower alkyl; Z = N, CH; Y = lower alkylene] or their salts, useful for prevention or treatment of heart and/or circulation disorders, are prepd. by oxidn. of R1aNHXYCONHCHR2CHR3OH (R1a = protecting group; R2, R3, X, Y = same as above) or their salts, followed by optional deprotection. Oxidn. of 905 mg 2-[5-[(benzyloxycarbonyl)amino]-2-(4-fluorophenyl)-1,6-dihydro-6-oxo-1-pyrimidinyl]-N-[2-(4,4,4-trifluoro-3-hydroxy-1-phenyl)butyl]acetamide with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-1-(1H)-one at room temp. for 15 h in CH2Cl2 gave 644 mg the corresponding ketone deriv., which inhibited **chymase** at IC50 of <1.0 .times. 10-5 M.

L13 ANSWER 31 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:95315 CAPLUS
DOCUMENT NUMBER: 128:175973
TITLE: Heterogeneity of mast cells in mastocytosis and **inhibitory** effect of ketotifen and ranitidine on indolent systemic mastocytosis
AUTHOR(S): Kurosawa, Motohiro; Amano, Hiroo; Kanbe, Naotomo; Akimoto, Sachiko; Takeuchi, Yuko; Yamashita, Tetsuji; Hashimoto, Tsutomu; Kurimoto, Fumihiko; Miyachi, Yoshiki
CORPORATE SOURCE: Dep. Dermatology, Gunma Univ. School Med., Maebashi, Japan
SOURCE: Journal of Allergy and Clinical Immunology (1997), 100(6, Pt. 2), S25-S32
CODEN: JACIBY; ISSN: 0091-6749
PUBLISHER: Mosby-Year Book, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mastocytosis is a disorder of mast cell proliferation that occurs in both cutaneous and systemic forms. The most frequent site is the skin. The mast cell subtype of two patients with mastocytosis was investigated. Methods: Immunohistochem. studies were performed on the skin or gastric mucosa or both of the two patients. **Blood** and urine levels of various mediators were measured for one patient. Mast cells contg. tryptase and **chymase** were the only type seen in the skin lesions of an 11-mo-old boy with urticaria pigmentosa. Mast cells contg. tryptase were predominant in lesions of the skin and gastric mucosa of a 41-yr-old man with indolent systemic mastocytosis. However, mat cells contg. tryptase and **chymase** were predominant in the nonlesional and the

normal skin of this patient. Tryptase-pos. cells were more numerous in lesional skin than nonlesional skin and normal skin. Elevated **blood** and urine levels of various mediators were decreased by means of combination therapy wit ketotifen and ranitidine. In indolent systemic mastocytosis, mast cell dynamics involve only cells may be inhibited by means of combination therapy with histamine H1 and H2 receptor antagonists.

L13 ANSWER 32 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:633080 CAPLUS
DOCUMENT NUMBER: 127:328114
TITLE: Characterization of **chymase** from human **vascular** tissues
AUTHOR(S): Takai, Shinji; Shiota, Naotaka; Sakaguchi, Masato; Muraguchi, Hiroko; Matsumura, Eiko; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki, 569, Japan
SOURCE: Clinica Chimica Acta (1997), 265(1), 13-20
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A chymostatin-sensitive angiotensin II-generating enzyme was found in human gastroepiploic arteries. The enzyme was purified using heparin affinity and gel filtration columns. The mol. wt. of the purified enzyme was 30 kDa, and the optimum pH was 7.5-9.0. Enzyme activity was inhibited by soybean trypsin **inhibitor**, phenylmethylsulfonyl fluoride, and chymostatin, but not by EDTA, pepstatin, or aprotinin. The enzyme rapidly converted angiotensin I to angiotensin II (Km = 67 .mu.M; Vmax, 43 pmol/s; kcat = 65/s), but did not hydrolyze angiotensin II, substance P, bradykinin, vasoactive intestinal peptide, LH-releasing hormone, somatostatin, or .alpha.-MSH. The N-terminal sequence was identical to the sequence for human skin/heart **chymase**. Thus, the chymostatin-sensitive angiotensin II-generating enzyme in human **vascular** tissues was identified as **chymase**.

L13 ANSWER 33 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:579734 CAPLUS
DOCUMENT NUMBER: 127:258646
TITLE: Gene specific universal mammalian sequence-tagged sites
INVENTOR(S): Brewer, George J.; Venta, Patrick J.; Yuzbasiyan-Gurkan, Vilma
PATENT ASSIGNEE(S): Regents of the University of Michigan, USA; Board of Trustees Operating Michigan State University; Brewer, George J.; Venta, Patrick J.; Yuzbasiyan-Gurkan, Vilma
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9731012	A1	19970828	WO 1997-US2403	19970218

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,

MR, NE, SN, TD, TG
AU 9719598 A1 19970910 AU 1997-19598 19970218
PRIORITY APPLN. INFO.: US 1996-12061P P 19960222
WO 1997-US2403 W 19970218

AB Primer sets which amplify conserved regions of specific genes across mammalian species are provided. Such genetic markers based on PCR primers are called sequence-tagged sites (STSs) or sequence-tagged site primers. Because the primer sets may be used to locate genes across mammalian species, such primer sets are referred to as universal mammalian sequence-tagged site (UM-STS) primers. The methods used to design the primer sets as well as methods of making and using the primer sets are also provided. Primers were designed to genes where the intron-exon structure was known in at least one species and where the nucleotide sequence was known in at least two species (the index species) that were not closely related. Tandemly duplicated genes known to have undergone gene conversion in any species were avoided. Primers were generally designed so that the amplified product contained an intron. Primers were designed to highly conserved nucleotide sequences contained within coding regions, and addnl. considerations taken into account were: degeneracy of underlying codons, placement of the 3' end of the primer with respect to amino acid mutability, and conservation of amino acids within multigene families when possible. All sets of primer pairs were designed to have approx. the same annealing temp. in anticipation of performing multiplex amplifications. The universal utility of these primers was studied on the DNAs from mammals representing several different orders using the primer sets under the reaction conditions (termed Zoo PCRs) that were found to amplify canine sequences.

L13 ANSWER 34 OF 61 CAPLUS
ACCESSION NUMBER: 1997:460877 CAPLUS
DOCUMENT NUMBER: 127:146360
TITLE: Purification and characterization of a kinin- and angiotensin II-forming enzyme in the dog heart
AUTHOR(S): Sasaguri, Manabu; Maeda, Hirokazu; Noda, Keita; Tsuji, Emiko; Kinoshita, Akio; Ideishi, Munehito; Ogata, Shigenori; Arakawa, Kikuo
CORPORATE SOURCE: Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, 814-80, Japan
SOURCE: Journal of Hypertension (1997), 15(6), 675-682
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A kinin-forming enzyme of dog heart was purifed and characterized and its ability to generate angiotensin (Ang) II from Ang I was examd. The enzyme was isolated from heart homogenate using a DEAE-Sepharose column, an aprotinin affinity column, and a wheat germ lectin-Sepharose 6MB column. Kininogenase activity was assessed with a kinin RIA after samples had been incubated with bovine low-mol.-wt. (LMW)-kininogen at 37.degree. for 1 h. The Ang I-converting activity was assessed by quantitation of Ang II formed by incubation of the sample with Ang I at 37.degree. for 3 h, using HPLC. The enzyme was subjected to 12.5% SDS-PAGE, stained by Coomassie Brilliant Blue, and transferred elec. to a membrane with glycoprotein staining. The purified enzyme was a glycoprotein with an apparent mol. wt. of 65 kDa by SDS-PAGE. Its kininogenase activity was .apprx.20 .mu.g bradykinin/h/mg protein at an optimal pH of 8.0. The enzyme also converted Ang I to Ang II at an optimal pH of 6.5. Its specific activity was .apprx.2 .mu.g Ang II/h/mg protein. Both activities were inhibited by aprotinin, a tissue kallikrein **inhibitor**. Western blot anal. using polyclonal antibody against this enzyme demonstrated that this enzyme exists both in the myocardium and in the **coronary** artery. The present study showed that the kinin-forming enzyme of dog heart was a kallikrein-like enzyme that was different from cathepsin D, cathepsin G,

and **chymase**. It was also able to convert Ang I to Ang II. This enzyme might play a role in regulating myocardial perfusion, mainly by generating kinins and in part by forming Ang II.

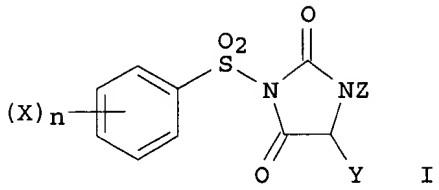
L13 ANSWER 35 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:315668 CAPLUS
DOCUMENT NUMBER: 127:48217
TITLE: Sheep mast cell proteinase-1, a serine proteinase with both tryptase- and **chymase**-like properties, is inhibited by plasma proteinase **inhibitors** and is mitogenic for bovine pulmonary artery fibroblasts
AUTHOR(S): Pemberton, Alan D.; Belham, Christopher M.; Huntley, John F.; Plevin, Robin; Miller, Hugh R. P.
CORPORATE SOURCE: Dep. of Veterinary Clinical Studies, Royal (Dick) School of Veterinary Studies, University of Edinburg, Veterinary Field Station, Midlothian, EH25 9RG, UK
SOURCE: Biochemical Journal (1997), 323(3), 719-725
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sheep mast cell proteinase-1 (sMCP-1), a serine proteinase with dual **chymase**/tryptase activity, is expressed in gastrointestinal mast cells, and released systemically and on to the mucosal surface during gastrointestinal nematode infection. The potential for native plasma proteinase **inhibitors** to control sMCP-1 activity was investigated. Sheep .alpha.1-proteinase **inhibitor** (.alpha.1PI) inhibited sMCP-1 slowly, with second-order assocn. rate const. (kass) 1.1 .times. 103 M-1.cntdot.s-1, whereas sheep contrapsin inhibited trypsin (kass 2.2 .times. 106 M-1.cntdot.s-1) but not sMCP-1. Western-blot anal. and gel filtration showed that when added to serum or plasma, sMCP-1 was partitioned between .alpha.1PI and .alpha.2-macroglobulin. The possibility that significant cleavage of plasma proteins could occur before sMCP-1 was inhibited was investigated using gel filtration and SDS-PAGE after adding sMCP-1 to plasma. Cleavage of ovine fibrinogen occurred in the presence of excess .alpha.1PI and .alpha.2-macroglobulin, the .alpha.-chain being cleaved C-terminally and the .beta.-chain at the putative Lys-27. In addn., sMCP-1 was mitogenic for bovine pulmonary artery fibroblasts, but was not mitogenic in the presence of soya-bean trypsin **inhibitor**. In terms of fibrinogen cleavage and fibroblast stimulation, sMCP-1 shows functional similarities to mast cell tryptase.

L13 ANSWER 36 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:189919 CAPLUS
DOCUMENT NUMBER: 126:212145
TITLE: Preparation of hydantoin derivatives as cardiovascular agents
INVENTOR(S): Fukami, Jiichi; Tsunoda, Motoo; Niwada, Shinjiro; Okada, Akiko; Sumya, Saki; Saito, Masayuki; Suzuki, Kenji; Kiso, Yoshinobu
PATENT ASSIGNEE(S): Suntory Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09031061	A2	19970204	JP 1995-216437	19950724

09/ 869,360

OTHER SOURCE(S): MARPAT 126:212145
GI



I

AB The title compds. (I; X = halo, C1-4 alkyl, etc.; n = 0-5; Z = H, aralkyl, C1-4 alkyl, etc.; Y = substituted aralkyl, alkoxyalkyl, etc.) are prepd. I, possessing **chymase inhibitory**, are useful for prevention and treatment of diabetes, **arteriosclerosis**, **hypertension**, circulatory system diseases, and cardiovascular diseases resulting from the increase of angiotensin II prodn. Thus, L-phenylalanine was reacted with 4-ClC6H4SO2NCO and then reacted with ClCO2Et in the presence of Et3N to give 23% I (Y = C6H4CH2, Z = H, Xn = 4-Cl), which showed IC50 of 8.5 .mu.M and 5.8 .mu.M against **chymase** and cathepsin G resp.

L13 ANSWER 37 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:88067 CAPLUS
DOCUMENT NUMBER: 126:181737
TITLE: Functional and biochemical analysis of angiotensin II-forming pathways in the human heart
AUTHOR(S): Wolny, Arlene; Clozel, Jean-Paul; Rein, Josiane; Mory, Paul; Vogt, Paul; Turino, Marko; Kiowski, Wolfgang; Fischli, Walter
CORPORATE SOURCE: Pharma Division, F. Hoffmann-La Roche Ltd., Basel, Switz.
SOURCE: Circulation Research (1997), 80(2), 219-227
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Blockade of the renin-angiotensin system by inhibition of angiotensin-converting enzyme (ACE) is beneficial for the treatment of **hypertension** and congestive heart failure. However, it is unclear how complete the blockade by ACe **inhibitors** is and if there is continuing angiotensin II (Ang II) formation during chronic treatment with ACE **inhibitors**. Indeed **chymase**, a serine proteinase, which is able to form angiotensin II from angiotensin I (Ang I) and cannot be blocked by ACE **inhibitors**, has been shown to be present in human heart. The goal of the present study was to evaluate the extent of renin-angiotensin system blockade and the Ang II-forming pathways in cardiac tissue of patients chronically treated with ACE **inhibitors** or in patients without ACE inhibition therapy. Our studies indicate an incomplete ACE inhibition in human heart tissue after chronic ACE **inhibitor** therapy. Moreover, ACE contributes only a small portion to the total Ang I conversion, as shown in biochem. studies in ventricular and **coronary** homogenates or functionally as Ang I contractions in isolated rings of **coronary** arteries. A serine proteinase was responsible for the majority of Ang II prodn. in both the membrane prepn. and Ang I-induced contractions of isolated **coronary** arteries. In humans, the serine proteinase pathway is likely to play an important role in cardiac Ang II formation. Thus, drugs such as renin **inhibitors** and Ang II receptor blockers might be able to induce a more complete blockade of the renin-angiotensin system, providing a more

efficacious therapy.

L13 ANSWER 38 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:552775 CAPLUS
DOCUMENT NUMBER: 125:239237
TITLE: Angiotensin II formation in dog heart is mediated by different pathways in vivo and in vitro
AUTHOR(S): Balcells, Eduardo; Meng, Qing C.; Hageman, Gilbert R.; Palmer, Ronald W.; Durand, Joan N.; Dell'Italia, Louis J.
CORPORATE SOURCE: Dep. Med., Univ. Alabama, Birmingham, AL, 35294, USA
SOURCE: American Journal of Physiology (1996), 271(2, Pt. 2), H417-H421
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiotensin-converting enzyme (ACE) **inhibitors** (I) have beneficial effects that are presumably mediated by decreased angiotensin II (ANG II) prodn. However, in vitro assays in human heart exts. have demonstrated that >75% of ANG II-forming enzyme activity was not inhibited by captopril (Cap) and therefore did not appear to be related to ACE but was inhibited by chymostatin, suggesting that it was predominantly **chymase**-like activity. Previous work in our lab. has demonstrated a similar relative contribution of ACE and **chymase**-like activity toward ANG II formation in vitro in dog heart tissue exts. Accordingly, we compared Cap-inhibitable ANG II formation in vitro in heart tissue of five adult mongrel dogs to the in vivo Cap-inhibitable, ANG II-forming activity across the myocardial bed in four open-chest, adult mongrel dogs. In vitro studies demonstrated that only 6% of ANG II formation was inhibited by Cap from heart tissue exts. of the left ventricular midwall. In the in vitro studies, ANG I (0.5 nmol/min) followed by ANG I plus the ACE **inhibitor** Cap (0.1 .mu.mol/min) was infused into the left anterior descending artery, and ANG II was assayed in the proximal aorta and **coronary** sinus. The arterial-venous (A-V) difference of ANG II across the myocardial circulation increased significantly during ANG I infusion (13.4 to 142.8 pg/mL). Subsequent coinfusion of Cap with ANG I significantly decreased the myocardial A-V difference of ANG II by 60%. Thus, in contrast to the in vitro situation, ANG II formation in vivo is inhibited significantly by Cap in the normal dog heart. This comparison of in vivo and in vitro conversion of ANG I to ANG II by ACE and **chymase**-like activity suggests that in vitro assays may underest. the functional contribution of ACE to intracardiac ANG II formation.

L13 ANSWER 39 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:487465 CAPLUS
DOCUMENT NUMBER: 125:165614
TITLE: Characterization, application and potential uses of biotin-tagged **inhibitors** for lymphocyte serine proteases (granzymes)
AUTHOR(S): Winkler, Ulrike; Allison, N. Janine; Woodard, Susan L.; Gault, Ruth A.; Ewoldt, Gerald R.; Kam, Chih-Min; Abuelyaman, Ahmed; Powers, James C.; Hudig, Dorothy
CORPORATE SOURCE: Dep. Microbiol. Sch. Veterinary Med., Univ. Nevada, Reno, NV, 89557-0046, USA
SOURCE: Molecular Immunology (1996), 33(7/8), 615-623
CODEN: MOIMD5; ISSN: 0161-5890
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytotoxic lymphocytes and natural killer cells are able to kill their target cells in minutes. The death of the target cell occurs after the release of cytoplasmic granules from the effector cell. These granules

contain the pore-forming protein perforin and serine proteases (granzymes). To date 10 genes encoding lymphocyte granzymes have been discovered; of these only four have been purified and characterized for their substrate specificity. Several are predicted to have a common **chymase**-like specificity which is found in the granule exts. Others may need to be enriched as active enzymes before they can be evaluated for substrate hydrolysis. Due to the limitations of detection by substrate hydrolysis, a more sensitive method for the detection of dil. granules was needed. We report the differing reactivities of seven biotin (Bi)-tagged isocoumarin (IC) **inhibitors** for Asp-ase, **chymase**, tryptase and Met-ase granzymes. The **inhibitors** contained different substituents at their no. 3 position: methoxy (OMe), ethoxy (OEt), propoxy (OPr) or 2-phenylethoxy (OEtPh) groups. The OMe group conferred general reactivity, whereas the OEtPh group conferred selective reactivity with **chymase** granzymes. The **inhibitors** that contained the longest aminocaproyl (Aca) spacers between the biotin-tag and the isocoumarin ring mediated the most stable granzyme inactivation. These **inhibitors** were the most effective at blocking lysis of red **blood** cells by the granule exts. The **inhibitors** were used in protein blotting expts. where the biotin was detected with an avidin-enzyme complex. Over 10 granzymes were labeled by the **inhibitor** Bi-Aca-Aca-IC-OMe. The **inhibitors** detected granzymes when they were not readily detected by substrate hydrolysis.

L13 ANSWER 40 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:314235 CAPLUS
DOCUMENT NUMBER: 125:6578
TITLE: **Chymase** in exocytosed rat mast cell granules effectively proteolyzes apolipoprotein AI-containing lipoproteins, so reducing the cholesterol efflux-inducing ability of serum and aortic intimal fluid
AUTHOR(S): Lindstedt, Leena; Lee, Miriam; Castro, Graciela R.; Fruchart, Jean-Charles; Kovanen, Petri T.
CORPORATE SOURCE: Wihuri Research Institute, Helsinki, 00140, Finland
SOURCE: Journal of Clinical Investigation (1996), 97(10), 2174-2182
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Degranulated mast cells are present in human fatty streaks. **Chymase** in granules released from degranulated rat serosal mast cells, i.e., in granule remnants, proteolyzes human high d. lipoprotein3 (HDL3), and so reduces its ability to induce cholesterol efflux from macrophage foam cells in vitro. In this study we found that remnant **chymase**, by proteolyzing human serum and human aortic intimal fluid, prevents these two physiol. fluids from effectively inducing cholesterol efflux from cultured macrophage foam cells. Inhibition was strongest when remnants were added to apolipoprotein AI (apoAI)-contg. lipoproteins; the remnants had no effect on the weaker efflux produced by apoAI-deficient serum. Western blot anal. showed that granule remnants degrade apoAI in serum and in intimal fluid. When released from remnants, **chymase** lost its ability to proteolyze HDL3 in the presence of serum. Thus, remnant **chymase** (but not isolated **chymase**) was able to resist the natural protease **inhibitors** present in serum and in intimal fluid. The results imply participation of exocytosed mast cell granules in foam cell formation in atherogenesis.

L13 ANSWER 41 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:90349 CAPLUS
DOCUMENT NUMBER: 124:139538

09/ 869,360

TITLE: Purification and characterization of angiotensin II-generating **chymase** from hamster cheek pouch
AUTHOR(S): Takai, Shinji; Shiota, Naotaka; Yamamoto, Daisuke; Okunishi, Hideki; Miyazaki, Mizuo
CORPORATE SOURCE: Department Pharmacology, Osaka Medical College, Takatsuki, 569, Japan
SOURCE: Life Sciences (1996), 58(7), 591-7
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hamster cheek pouch **vascular** tissues contain an angiotensin II-forming enzyme which is inhibited by chymostatin but not by any angiotensin-converting enzyme **inhibitors**. The enzyme was purified to apparent homogeneity by gel filtration and heparin-Sepharose affinity chromatog. The mol. mass estd. by SDS-PAGE was 28 kDa and the optimum pH was between 7.5 and 9.0. The angiotensin II-forming activity was inhibited by chymostatin, soybean trypsin **inhibitor** and phenylmethylsulfonyl fluoride, but not by aprotinin. The N-terminal sequence showed high homol. with chymases from various species. Thus, the angiotensin II-generating enzyme obtained from hamster cheek pouch vessels is a **chymase**.

L13 ANSWER 42 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:631372 CAPLUS
DOCUMENT NUMBER: 121:231372
TITLE: Preparation of peptide **inhibitors** of angiotensin I **chymase**(s) including human heart **chymase**
INVENTOR(S): Hoover, Dennis J.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9325574	A1	19931223	WO 1993-US3625	19930423
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 644892	A1	19950329	EP 1993-909587	19930423
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1992-897723 19920612
WO 1993-US3625 19930423
OTHER SOURCE(S): MARPAT 121:231372
AB R4ADCHR3COXNHCHY[(CH2)nR1] [R1 = (substituted) Ph, naphthyl, cycloalkyl, (benzo-fused) unsatd. heterocyclyl; R3 = (substituted) alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl, Ph, unsatd. heterocyclyl(alkyl), phenylalkyl; R4 = (substituted) piperazino, piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl, azetidino, 4-morpholino, 4-thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, alkyl, cycloalkyl, etc.; A = CO, SO2; D = (alkyl)imino, (alkyl)methylene, O, CH(OH); X = (substituted) proline, 2-piperidinecarboxylic acid, 2-azetidinecarboxylic acid residue; Y = BF2, B(OM)2, COZ, C(OH)2Z; M = H, alkyl; B(OM)2 = satd. heterocyclyl; Z = CF2R11, CF2CONR12R13, CO2R12, (substituted) heterocyclyl; R11 = H, F, alkyl, perfluoroalkyl, aminoalkyl, alkylaminoalkyl, alkoxyalkyl, hydroxyalkyl; R12, R13 = H, alkyl, alkenyl, etc.], were prepd. Title compds. are effective for treating or preventing **hypertension**,

congestive heart failure, myocardial infarction, cardiac and left ventricular hypertrophy, **coronary** artery disease including myocardial infarction, **vascular** hypertrophy, and **vascular** damage following diabetic and non-diabetic renal disease, and **vascular** damage assocd. with **angioplasty** and aetheroma (no data). Thus, N-[(1,1-dimethylethoxy)carbonyl]phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]prolinamide was prepd. in several steps from 3(S,R)-N-[(1,2-dimethylethoxy)carbonyl]-3-amino-2-hydroxy-4-phenylbutyronitrile.

L13 ANSWER 43 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:571329 CAPLUS
DOCUMENT NUMBER: 121:171329
TITLE: Vasoconstrictor action of angiotensin I--convertase and the synthetic substrate (Pro11, d-Ala12)-angiotensin I
AUTHOR(S): Mangiapane, Michael L.; Rauch, Albert L.; MacAndrew, Joseph T.; Ellery, Suzanne S.; Hoover, Karen W.; Knight, Delvin R.; Johnson, Holly A.; Magee, William P.; Cushing, Daniel J.; Buchholz, R. Allan
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc, Groton, CT, 06340, USA
SOURCE: Hypertension (Dallas) (1994), 23(6, Pt. 2), 857-60
CODEN: HPRTDN; ISSN: 0194-911X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A **chymase** (also referred to as angiotensin I-convertase) specific for the conversion of angiotensin (Ang) I to Ang II has been identified in human heart. This serine protease is also present in dog and marmoset vasculature. The authors examd. the vasoconstrictor effects of Ang II putatively generated from an angiotensin-converting enzyme (ACE)-resistant convertase synthetic substrate (SUB) in vivo and in vitro. In marmosets, SUB (7 to 700 .mu.g/kg IV) or Ang I (0.1 to 30 .mu.g/kg) caused similar dose-dependent increases in mean arterial pressure (10 to 100 mm Hg) and decreases in heart rate. Pressor effects of SUB were slightly attenuated at low (but not high) doses by captopril (CAP, 1 mg/kg IV) and blocked by losartan (5 mg/kg IV); in contrast Ang I pressor effects were substantially blocked by both. In isolated canine superior mesenteric artery, Ang I-induced contraction was eliminated by losartan and reduced but not eliminated by 10 .mu.mol/L CAP. When combined with the serine protease **inhibitor** chymostatin, CAP eliminated Ang I-induced contraction, but chymostatin alone had no effect. SUB-induced contraction was not blocked by CAP but was equally blocked by chymostatin (25 .mu.mol/L) alone or by the combination of CAP (10 .mu.mol/L) and chymostatin (25 .mu.mol/L); losartan (10 .mu.mol/L) eliminated SUB-induced responses. Previous studies have suggested that Ang I-convertase is important for prodn. of Ang II in the heart. The results are consistent with a potential role for Ang I-convertase in the prodn. of Ang II in the vasculature, resulting in Ang II-mediated vasoconstriction.

L13 ANSWER 44 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:293022 CAPLUS
DOCUMENT NUMBER: 120:293022
TITLE: Serine proteases resistant to their physiological **inhibitors**
INVENTOR(S): Dawson, Keith Martyn; Gilbert, Richard James
PATENT ASSIGNEE(S): British Bio-Technology Ltd., UK
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9403614	A1	19940217	WO 1993-GB1632	19930803
W: AU, CA, CZ, DE, ES, FI, GB, HU, JP, KR, NO, NZ, RU, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 658206	A1	19950621	EP 1993-917972	19930803
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 07509610	T2	19951026	JP 1993-505114	19930803
ZA 9305660	A	19940317	ZA 1993-5660	19930814
ES 2080657	B1	19961101	ES 1993-2039	19930927
ES 2080657	A1	19960201		
US 5645833	A	19970708	US 1995-379621	19950203
US 5932213	A	19990803	US 1997-889078	19970707
PRIORITY APPLN. INFO.:			GB 1992-16558	19920804
			WO 1993-GB1632	19930803
			US 1995-379621	19950203

AB Serine proteases of the chymotrypsin superfamily are modified so that they exhibit resistance to their cognate physiol. **inhibitors**. This is achieved by disrupting the surface of the enzyme to which the **inhibitor** binds using 3D models of proteins and sequence similarities to identify important residues. If such modified serine proteases have fibrinolytic, thrombolytic, antithrombotic or prothrombotic properties, they are useful in the treatment of **blood** clotting diseases or conditions. The prepn. of antiplasmin resistant analogs of plasmin is demonstrated.

L13 ANSWER 45 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:208658 CAPLUS
DOCUMENT NUMBER: 120:208658
TITLE: Cardiac angiotensin II formation: the angiotensin-I converting enzyme and human **chymase**
AUTHOR(S): Urata, H.; Ganten, D.
CORPORATE SOURCE: Max-Delbrueck-Cent. Mol. Med., Berlin, 13125, Germany
SOURCE: Eur. Heart J. (1993), 14(Suppl. I), 177-82
CODEN: EHJODF; ISSN: 0195-668X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 50 refs., focussed on the novel cardiac Ang II-forming enzyme, human **chymase**, comparing it with the conventional enzyme angiotensin-I converting enzyme (ACE) in the heart. ACE **inhibitors** have provided a remarkable improvement in the treatment of patients with primary **hypertension** and congestive heart failure. The cardiac renin-angiotensin system is one of the major targets of ACE **inhibitor** therapy since recent studies show that the human heart contains high affinity angiotensin II (Ang II) receptors and ACE activity. However, it is not clear why ACE **inhibitors** are more effective than other vasodilators in the treatment of patients with congestive heart failure. This gap in knowledge led the authors to study the biochem. mechanism of Ang II formation in the human heart. Such studies have only recently been addressed. So far, two Ang II-forming enzymes (ACE and human **chymase**) have been identified. Unlike in the rat heart, the minor (10%) component of Ang II-forming activity in the left ventricle is due to ACE, whereas the major (80%) component is due to human **chymase**. This novel cardiac serine proteinase has been purified from the human left ventricle and characterized, and recently, the cDNA and the gene for this enzyme have been cloned. Biochem. characterization revealed that human **chymase** is the most efficient and specific Ang II-forming enzyme described thus far, but the cellular and regional distribution of two Ang II-forming enzymes seem to be quite different. ACE is localized mainly in endothelial cells and its expression level is higher in atria than ventricles whereas **chymase** is localized in the interstitial region of the myocardium

and its expression is higher in ventricles than atria. These results imply distinct roles of these two Ang II-forming enzymes in cardiac Ang II formation and in the physiol. function of the human heart. Ang II formation by **chymase**, independent of ACE, may play an important role in the beneficial effect of ACE **inhibitor** therapy for patients with congestive heart failure.

L13 ANSWER 46 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:127904 CAPLUS
DOCUMENT NUMBER: 120:127904
TITLE: Proteolysis and fusion of low density lipoprotein particles independently strengthen their binding to exocytosed mast cell granules
AUTHOR(S): Paananen, Katariina; Kovanen, Petri T.
CORPORATE SOURCE: Wihuri Res. Inst., Helsinki, SF-00140, Finland
SOURCE: J. Biol. Chem. (1994), 269(3), 2023-31
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Contact between low d. lipoproteins (LDL) and exocytosed mast cell granules, the "granule remnants," leads to binding of LDL to the granule remnants via ionic interactions between the apolipoprotein B-100 (apoB-100) component of LDL and the heparin proteoglycan component of the granule remnants. Upon incubation at 37 .degree.C, the heparin proteoglycan-bound apoB-100 is progressively proteolyzed by remnant **chymase** and carboxypeptidase A, which are also bound to the heparin proteoglycans. Thereupon, the LDL particles fuse, and their binding to the granule remnants strengthens, as defined by the decreased ability of NaCl to release LDL from the remnants. The authors now have examd. sep. the effects of proteolysis and fusion on LDL binding. Proteolysis without fusion was induced by lowering the incubation temp. to 15 .degree.C, and proteolysis-independent fusion was induced by treating granule remnant-bound LDL with sphingomyelinase in the presence of protease **inhibitors**. It was found that degrdn. of the heparin proteoglycan-bound apoB-100, even without accompanying particle fusion, increased the strength of LDL binding to the granule remnants, suggesting exposure of buried heparin binding regions of apoB-100. When such proteolyzed LDL particles were allowed to fuse, the strength of their binding to the granule remnants increased still further, probably because of an increase in the no. of apoB-100 fragments in the enlarged particles. Proteolysis-independent fusion, induced by sphingomyelinase treatment of granule remnant-bound LDL, also increased the strength of binding. The results show that proteolytic degrdn. and fusion, the two modifications of granule remnant-bound LDL subsequent to action by **chymase** and carboxypeptidase A of the granule remnants, represent two sep. mechanisms by which LDL particles become tightly bound to the heparin proteoglycans of exocytosed mast cell granules. Since the formation of an atheroma, the hallmark of atherosclerosis, is characterized by accumulation in the proteoglycan matrix of the arterial intima of extracellular **lipid** droplets resembling the fused LDL particles on the granule remnant surfaces, the modifications of LDL described in this study may provide a clue to the actual processes by which the **lipid** droplets are anchored to the arterial intima.

L13 ANSWER 47 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:26175 CAPLUS
DOCUMENT NUMBER: 120:26175
TITLE: Comparative studies of the Spi1 proteins of three equine alpha-1-proteinase **inhibitor** haplotypes following isolation by affinity chromatography
AUTHOR(S): Pemberton, A. D.; Miller, H. R. P.; John, H. A.; Scudamore, C. L.

09/ 869,360

CORPORATE SOURCE: Moredun Res. Inst., Edinburgh, UK
SOURCE: Int. J. Biochem. (1993), 25(9), 1263-8
CODEN: IJBOBV; ISSN: 0020-711X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antiproteinase deficiency can result in excessive proteinase-induced tissue damage. The major anti-elastase (Spi1) protein of equine .alpha.1-proteinase **inhibitor** (.alpha.1-PI) was isolated from the plasma/serum of 3 common haplotypes (I, L and U). The N-terminal amino acid sequences of the 3 **inhibitors** were identical, but were only approx. 65-77% homologous with two other published equine Spi1 sequences. All three **inhibitors** complexed quickly and irreversibly with equine leukocyte proteinase 2A (kass = 2 .times. 107 M-1 sec-1). They were also efficient **inhibitors** of **chymase** (rat mast cell proteinase-II; kass = 2 .times. 105 M-1 sec-1; Ki = 2 .times. 10-10 M). There was therefore no evidence of deficient inhibition in the Spi1 variants of the I, L and U haplotypes.

L13 ANSWER 48 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:401703 CAPLUS
DOCUMENT NUMBER: 119:1703
TITLE: Cellular localization and regional distribution of an angiotensin II-forming **chymase** in the heart
AUTHOR(S): Urata, Hidenori; Boehm, Keith D.; Philip, Annie; Kinoshita, Akio; Gabrovsek, Janez; Bumpus, F. Merlin; Husain, Ahsan
CORPORATE SOURCE: Dep. Cardiovasc. Biol., Cleveland Clin. Found., Cleveland, OH, 44195, USA
SOURCE: J. Clin. Invest. (1993), 91(4), 1269-81
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human heart **chymase** has recently been purified and its cDNA and gene cloned. This cardiac serine proteinase is the most efficient and specific angtiotensin II (Ang II)-forming enzyme described. To obtain insights into the cardiac sites of **chymase**-dependent Ang II formation, the authors examd. the cellular localization and regional distribution of **chymase** in the human heart. Electron microscope immunocytochem. using an anti-human **chymase** antibody showed the presence of **chymase**-like immunoreactivity in the cardiac interstitium and in cytosolic granules of mast cells, endothelial cells, and some mesenchymal interstitial cells. In the cardiac interstitium, **chymase**-like immunoreactivity is assocd. with the extracellular matrix. In situ hybridization studies further indicated that **chymase** mRNA is expressed in endothelial cells and in interstitial cells, including mast cells. Tissue **chymase** levels were detd. by activity assays and by Western blot analyses. **Chymase** levels were approx. 2-fold higher in ventricles than in atria. There were no differences in **chymase** levels in ventricular tissues obtained from nonfailing donor hearts, failing ischemic hearts, or hearts from patients with ischemic cardiomyopathy. These findings suggest that a major site of **chymase**-dependent Ang II formation in the heart is the interstitium and that cardiac mast cells, mesenchymal interstitial cells, and endothelial cells are the cellular sites of synthesis and storage of **chymase**. In the human heart, because ACE levels are highest in the atria and **chymase** level are highest in ventricles, it is likely that the relative contribution of ACE and **chymase** to cardiac Ang II formation varies with the cardiac chamber. Such differences may lead to differential suppression of cardiac Ang II levels during chronic ACE **inhibitor** therapy in patients with congestive heart failure.

L13 ANSWER 49 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:527381 CAPLUS
DOCUMENT NUMBER: 117:127381
TITLE: An amyloid hydrolysing proteinase from human tissue
INVENTOR(S): Dovey, Harry F.; Seubert, Peter A.; Sinha, Sukanto; McConlogue, Lisa; Little, Sheila P.; Johnstone, Edward M.
PATENT ASSIGNEE(S): Athena Neurosciences, Inc., USA; Lilly, Eli, and Co.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9207068	A1	19920430	WO 1991-US7290	19911004
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5292652	A	19940308	US 1991-766351	19910930
PRIORITY APPLN. INFO.:			US 1990-594122	19901005
			US 1991-766351	19910930

AB An proteinase that cleaves Met-Asp bonds in amyloid protein-like substrates is purified from human **blood** and brain tissue. Antibodies to the protein are prepd. and a cDNA for the enzyme is cloned. The protein was purified from clarified brain homogenates by ion-exchange and gel filtration chromatog.to yield a protein of 80,000 mol. wt. free of contaminating proteinases. The enzyme is inhibited by EDTA and to some extent by serine proteinase **inhibitors**. The enzyme appears to be distinct from clipsin. Immunohistol. of the enzyme showed assocn. with pathol. changes in Alzheimer's disease brain. The cDNA was cloned using amino acid sequence-derived oligonucleotide probes to screen a normal human brain cDNA bank in .lambda.gt10.

L13 ANSWER 50 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:210228 CAPLUS
DOCUMENT NUMBER: 116:210228
TITLE: Chymotrypsin-like proteases associated with Alzheimer's disease and their **inhibitors**
INVENTOR(S): Siman, Robert; Nelson, Robert B.; Kauer, James C.; Potter, Huntington
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9113904	A1	19910919	WO 1991-US1474	19910304
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2077665	AA	19910906	CA 1991-2077665	19910304
AU 9174654	A1	19911010	AU 1991-74654	19910304
AU 661270	B2	19950720		
EP 518955	A1	19921223	EP 1991-905743	19910304
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
HU 62312	A2	19930428	HU 1992-2842	19910304
JP 05506777	T2	19931007	JP 1991-506146	19910304

EP 732399	A2	19960918	EP 1996-103933	19910304
EP 732399	A3	19970312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 9101607	A	19911224	ZA 1991-1607	19910305
FI 9203983	A	19920904	FI 1992-3983	19920904
NO 9203469	A	19921104	NO 1992-3469	19920904
PRIORITY APPLN. INFO.:			US 1990-489290	19900305
			EP 1991-905743	19910304
			WO 1991-US1474	19910304

OTHER SOURCE(S): MARPAT 116:210228

AB Two endopeptidases involved in Alzheimer's disease, which cleave between methionine and aspartic acid in a .beta.-amyloid precursor protein, are purified. from rat and human brain. These proteases are called **chymase** (aka mast cell protease I) and multicatalytic protease (aka ingensin, lens neutral endopeptidase, proteasome, and macropain). Substrates of these enzymes can be used for detection of the proteases; **inhibitors** can be used in treatment of Alzheimer's disease (no data). Peptide derivs. which are substrates or **inhibitors** of these proteases were synthesized and tested with the purified enzymes. **Chymase** activity was higher in brain regions affected by Alzheimer's disease than in those not known to be affected.

L13 ANSWER 51 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:166423 CAPLUS
DOCUMENT NUMBER: 116:166423
TITLE: Immunological characterization of rat kininogens with monoclonal antibodies to T-kininogen. Distinction between the different domains of T-kininogen and the multiple rat kininogens
AUTHOR(S): Lesage, Suzanne; Bouhnik, Jacob; Richoux, Jean Pierre; Baussant, Thierry; Gauthier, Francis; Eager, Kendra; Corvol, Pierre; Alhenc-Gelas, Francois
CORPORATE SOURCE: U36, INSERM, Paris, F-75005, Fr.
SOURCE: Eur. J. Biochem. (1992), 204(2), 501-8
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A panel of 16 monoclonal antibodies (mAb) were produced against rat T-kininogen to characterize this family of proteins. These mAbs bound 125I-T-kininogen by RIA as well as reacting strongly with immobilized T-kininogen in an ELISA. The reactivity of these antibodies with proteolytic fragments of T-kininogen demonstrated the recognition of several different epitopes. One antibody was specific for the domain 1 of the heavy chain and/or the light chain, 12 antibodies were specific for domain 2, and 3 antibodies were specific for domain 3. All monoclonal antibodies recognized the 2 forms of T-kininogen encoded by the 2 different T-kininogen genes, TI and TII kininogen, except antibody TK 16-3.1 which uniquely reacted with TII kininogen. Two antibodies recognizing domain 2 cross-reacted with the high-mol.-mass kininogen (H-kininogen), whereas all the other monoclonal antibodies were specific to T-kininogen and did not recognize the heavy chain of H-kininogen. None of the antibodies tested altered the thiol protease **inhibitory** activity of T-kininogen, its partial proteolysis by rat mast cell **chymase**, or the hydrolysis of H-kininogen by rat urinary kallikrein. The use of these antibodies in the development of sensitive ELISA to measure T-kininogen levels in plasma, urine, liver microsomes, and hepatocytes is described. Two different forms of T-kininogen were distinguished by these monoclonal antibodies in Western blotting using rat plasma. The localization of T-kininogen was defined using these monoclonal antibodies by immunohistochem. in rat liver hepatocytes and rat kidney.

L13 ANSWER 52 OF 61 CAPLUS COPYRIGHT 2002 ACS

09/ 869,360

ACCESSION NUMBER: 1992:103423 CAPLUS
DOCUMENT NUMBER: 116:103423
TITLE: Purification, detection, and methods of use of protease nexin-2
INVENTOR(S): Van Nostrand, William E.; Cunningham, Dennis D.; Wagner, Steven L.
PATENT ASSIGNEE(S): University of California, Oakland, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9116628	A1	19911031	WO 1991-US1971	19910325
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
EP 527823	A1	19930224	EP 1991-908640	19910325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05506990	T2	19931014	JP 1991-508302	19910325
US 5213962	A	19930525	US 1992-924417	19920730
US 5427931	A	19950627	US 1993-56423	19930427

PRIORITY APPLN. INFO.: US 1990-513786 19900424
WO 1991-US1971 19910325
US 1992-924417 19920730

AB Protease nexin-2 (PN-2) and .beta. amyloid precursor protein (.beta.APP) are immunopurified (using monoclonal antibody mAbP2-1-Sepharose), detected in **blood** platelets for diagnosing neurodegenerative conditions (e.g. Alzheimer's disease and Down's syndrome), and used in pharmaceuticals to treat and prevent amyloid plaque deposition and inhibit serine proteases and **blood**-coagulation factor XIa, etc. PN-2 may be modified by cloning and expression methods to lack at least a portion of the amyloid A4 region. PN-2 was immunopurified from normal human neonatal foreskin fibroblasts and partial amino acid sequences were detd. Identity was found within the deduced sequence for .beta.APP. Amino acid residue 27 of PN-2 was questionably Phe, rather than His of .beta.APP. The amino terminus of PN-2 started at position 18 of .beta.APP. PN-2 inhibited chymotrypsin and trypsin and trypsin-like proteases, including Factor XIa. Assays for PN-2/.beta.APP, studies of PN-2/.beta.APP release from platelets, detn. of normal levels of PN-2/.beta.APP in platelets and cerebrospinal fluid, and other studies are described. An injection for prevention of Alzheimer's contains PN-2/.beta.APP 2 mg/mL and sterile water.

L13 ANSWER 53 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:51907 CAPLUS
DOCUMENT NUMBER: 116:51907
TITLE: Rapid degradation of neurotensin by stimulated rat mast cells
AUTHOR(S): Cochrane, David E.; Carraway, Robert E.; Boucher, William; Feldberg, Ross S.
CORPORATE SOURCE: Dep. Biol., Tufts Univ., Medford, MA, 02155, USA
SOURCE: Peptides (Fayetteville, N. Y.) (1991), 12(6), 1187-94
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A RIA towards neurotensin (NT) using C-terminal- and N-terminal-specific antisera was used to study degrdn. of this tridecapeptide by isolated rat mast cells. Incubation of NT (10 .mu.M) with peritoneal or pleural mast cells resulted in a rapid loss of NT immunoreactivity (iNT), as measured by C-terminal-directed antiserum, with little effect on N-terminal iNT.

The rate of the reaction was faster with pleural cells (T1/2, 30 s) than with peritoneal cells (T1/2, 180 s) and was > 10-fold slower in the presence of metabolic poisons. The enzyme(s) involved is most likely released from the cells during secretion, as NT was degraded by media conditioned by compd. 48/80-stimulated mast cells 40-60 times faster than by media from unstimulated cells. This degrdn. by conditioned media was concn.-dependent, pH-dependent, and temp.-sensitive. HPLC analyses indicated a near stoichiometric conversion of NT to NT(1-12) (66%) and NT(1-11) (34%) after incubation for 10-30 s with conditioned media. By 30 min only NT(1-11) and NT(1-10) were present. Phenanthroline (1 mM), an **inhibitor** of carboxypeptidase, prevented the loss of C-terminal iNT and the generation of NT(1-12) and NT(1-11). While NT(1-12) was effective in releasing histamine from mast cells in vitro and increasing **vascular** permeability in vivo, NT(1-11) was not. These results suggest that carboxypeptidase-like enzyme(s) could modulate the level and form of NT-related peptides in various states involving activation of mast cells.

L13 ANSWER 54 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:159530 CAPLUS
DOCUMENT NUMBER: 114:159530
TITLE: Further studies on lipopolysaccharide-sensitive serine protease zymogen (factor C): its isolation from Limulus polyphemus hemocytes and identification as an intracellular zymogen activated by .alpha.-chymotrypsin, not by trypsin
AUTHOR(S): Tokunaga, Fuminori; Nakajima, Hiroshi; Iwanaga, Sadaaki
CORPORATE SOURCE: Fac. Sci., Kyushu Univ., Fukuoka, 812, Japan
SOURCE: J. Biochem. (Tokyo) (1991), 109(1), 150-7
CODEN: JOBIAO; ISSN: 0021-924X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intracellular serine protease zymogen, factor C (an initiator in the hemolymph coagulation system) was purified from the hemocytes of the American horseshoe crab, L. polyphemus. The objective was to compare its properties with those of the Japanese horseshoe crab, Tachypleus (T.) tridentatus, factor C. The purified zymogen L.-factor C showed similar properties to those of T.-factor C, in terms of mol. mass (123,000), amino acid compn. (1011 residues), subunit structure (two chains), and antigenicity. Like the zymogen T.-factor C, this zymogen was also activated autocatalytically in the presence of bacterial lipopolysaccharide (LPS) and its synthetic **lipid** A analog. A most interesting finding is that both protease zymogens are rapidly activated by .alpha.-chymotrypsin or rat mast cell **chymase**, but not by trypsin. The active enzyme factor C* showed .alpha.-thrombin-like specificity toward synthetic tripeptide substrates. This factor C* was also strongly inhibited by an .alpha.-thrombin **inhibitor**, D-Phe-Pro-Arg-chloromethyl ketone. Thus, the enzymic properties of factor C* are similar to those of mammalian .alpha.-thrombin. On the other hand, the coagulation cascade system in the hemocyte lysate was activated when chymotrypsin, free from LPS, was added to the lysate used to detect the endotoxins. The implication is that the chymotrypsin-catalyzed initiation of the horseshoe crab coagulation system is unique, since all known mammalian coagulation, fibrinolysis, and complement systems are initiated by trypsin-like enzymes.

L13 ANSWER 55 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:609610 CAPLUS
DOCUMENT NUMBER: 113:209610
TITLE: Anaphylatoxin binding and degradation by rat peritoneal mast cells. Mechanisms of degranulation and control

AUTHOR(S): Fukuoka, Yoshihiro; Hugli, Tony E.
CORPORATE SOURCE: Dep. Immunol., Res. Inst. Scripps Clin., La Jolla, CA, 92037, USA
SOURCE: J. Immunol. (1990), 145(6), 1851-8
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Incubation of radiolabeled human complement C3a with rat peritoneal mast cells resulted in high levels of uptake and extensive degrdn. of the ligand. Both cell-bound and free radiolabeled human C3a underwent extensive degrdn. by rat mast cells even at 0.degree.. The protease **inhibitors** PMSF, chymostatin, and soybean trypsin **inhibitor** were most effective in preventing radiolabeled human C3a degrdn. Degrdn. of the cell-bound ligand was totally inhibited only by PMSF. These compds. are effective **inhibitors** of a chymotrypsin-like enzyme (**chymase**) extd. from rat mast cells. Chem. crosslinking of radiolabeled human C3a to surface components on the rat mast cells, in the presence of PMSF, revealed one major and two minor bands. The mast cell component in both the major and minor bands proved to be **chymase**-assocd. based on a direct comparison with purified **chymase** isolated from rat mast cells. However, neither antichymase antibody nor **chymase inhibitors** influenced the degranulating activity of C3a on rat mast cells that occur independently of the C3a-**chymase** interactions. Therefore, there are neither specific C3a-binding sites on rat mast cells nor specific receptors whose occupancy leads to cellular activation. Although human C3ades Arg is inactive on guinea pig ileal and lung tissue, it binds to and induces degranulation of rat mast cells, as well as enhances **vascular** permeability in rat skin, at concns. nearly identical to that of intact C3a. The fact that both C3a and C3ades Arg stimulated mast cell activation, at concns. in excess of 10-6 M, argues against specific binding sites for the anaphylatoxin on rat mast cells. It is proposed that the cationic C3a mol. activates rat mast cells in a secretory and nonlytic manner by a nonspecific mechanism similar to that of other polybasic compds.

L13 ANSWER 56 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:609065 CAPLUS
DOCUMENT NUMBER: 113:209065
TITLE: .alpha.1-Antichymotrypsin is associated with amyloid in brain senile plaques in Alzheimer-type dementia.
AUTHOR(S): Shoji, Mikio
CORPORATE SOURCE: Sch. Med., Gunma Univ., Maebashi, 371, Japan
SOURCE: Shinkei Kenkyu no Shinpo (1990), 34(3), 430-40
CODEN: SKNSAF; ISSN: 0001-8724
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 48 refs. .alpha.1-Antichymotrypsin (ACT) is a glycoprotein with a mol. wt. of 64 kDa to 69 kDa in **blood** serum, liver, and brain. ACT consists of 433 amino acid residues, produced in liver and secreted into the **blood**. ACT is also formed in the brain. **Blood** ACT level is elevated in acute inflammation, infection and malignancies. ACT inhibits chymotrypsin like seryl protease, ie., cathepsin G, chymotrypsin, elastase and **chymase**. Immunocytochem. shows that ACT is present in neurons, and cortical/subcortical astrocytes. All types of senile plaques and some small amyloid deposits are labeled by ACT staining in Alzheimer brains. Subpial amyloid deposits are neg. Almost all the senile plaques, including diffuse plaques, are labeled by ACT staining. Neurofibrillary tangles also contain ACT. Diffuse plaques in Down's syndrome and amyloid angiopathy are also stained. However, Kuru plaques and amyloids in systemic amyloidosis are neg. Other serine protease **inhibitors** and a serine protease are neg. in senile plaques. This indicates that ACT

is closely related to senile plaque amyloids from early to late stages. Serum ACT is only elevated in Alzheimer-type dementia (ATD) patients. Thus, serum ACT is considered to be a biochem. marker of ATD.

L13 ANSWER 57 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:530511 CAPLUS
DOCUMENT NUMBER: 113:130511
TITLE: Mast cell **chymase** potentiates histamine-induced wheal formation in the skin of ragweed-allergic dogs
AUTHOR(S): Rubinstein, Israel; Nadel, Jay A.; Graf, Paul D.; Caughey, George H.
CORPORATE SOURCE: Cardiovasc. Res. Inst., Univ. California, San Francisco, CA, 94143, USA
SOURCE: J. Clin. Invest. (1990), 86(2), 555-9
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Skin mast cells release the neutral protease **chymase** along with histamine during degranulation. To test the hypothesis that **chymase** modulates histamine-induced plasma extravasation, wheal formation was measured following intradermal injection of purified mast cell **chymase** and histamine into the skin of ragweed-allergic dogs. **Chymase** greatly augments histamine-induced wheal formation. The magnitude of the potentiating effect increases with increasing doses of **chymase** and becomes maximal .apprx. 30 min after administration. Injection of **chymase** without histamine does not evoke wheal formation. The **chymase** potentiation of histamine-induced skin responses is prevented completely by pretreatment with skin responses is prevented completely by pretreatment with the H1-receptor antagonist pyrilamine, and is prevented by inactivation of **chymase** with soybean trypsin **inhibitor**, suggesting that both histamine and preserved catalytic activity are required for the effects of **chymase**. To examine the effects of histamine and **chymase** released in situ in further expts., wheal size was measured following local degranulation of mast cells by intradermal injection of ragweed antigen or compd. 48/80. Pretreatment with either soybean trypsin **inhibitor** or pyrilamine markedly reduces ragweed antigen- or 48/80-induced wheal formation, supporting the results obtained by injection of exogenous **chymase** and histamine. These findings suggest a novel and important proinflammatory role for **chymase** in modulating the effects of histamine on **vascular** permeability during mast cell activation.

L13 ANSWER 58 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:511430 CAPLUS
DOCUMENT NUMBER: 113:111430
TITLE: Immunopurification and protease **inhibitory** properties of protease nexin-2/amyloid .beta.-protein precursor
AUTHOR(S): Van Nostrand, William E.; Wagner, Steven L.; Farrow, Jeffrey S.; Cunningham, Dennis D.
CORPORATE SOURCE: Coll. Med., Univ. California, Irvine, CA, 92717, USA
SOURCE: J. Biol. Chem. (1990), 265(17), 9591-4
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protease nexin-2 (PN-2) is a protease **inhibitor** that is synthesized and secreted by a variety of extravascular cells including human fibroblasts. It was previously reported that PN-2 is the secreted form of the amyloid .beta.-protein precursor (APP) and is a potent **inhibitor** of chymotrypsin. Here a 2-step procedure was described to purify PN-2/APP using a monoclonal antibody immunoaffinity column. The

protease **inhibitory** properties of purified PN-2/APP on a no. of serine proteases were quantitated. PN-2/APP was a potent **inhibitor** of coagulation factor XIa with a Ki = 2.9 .times. 10-10. The inhibition of factor XIa by PN-2/APP was augmented by heparin and resulted in a Ki = 5.5 .times. 10-11 M. Trypsin and chymotrypsin were also effectively inhibited with a Ki = 4.2 .times. 10-10 and 1.6 .times. 10-9, resp. PN-2/APP also inhibited the epidermal growth factor binding protein, the .gamma.-subunit of nerve growth factor, and **chymase** and plasmin to a lesser extent. In view of recent findings that PN-2/APP is contained in .alpha.-granules of platelets and is secreted upon platelet activation, the potent inhibition of factor XIa suggests that PN-2/APP may play a regulatory role in the coagulation pathway at **vascular** wound sites. In addn., these studies define biochem. activities of PN-2/APP which may be involved in regulating proteases that lead to the generation and deposition of the B-protein in neurodegenerative lesions assocd. with Alzheimer's disease and Down's syndrome.

L13 ANSWER 59 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:610955 CAPLUS
DOCUMENT NUMBER: 111:210955
TITLE: Reaction of human skin chymotrypsin-like proteinase **chymase** with plasma proteinase **inhibitors**
AUTHOR(S): Schechter, Norman M.; Sprows, Jennifer L.; Schoenberger, Oeyvind L.; Lazarus, Gerald S.; Cooperman, Barry S.; Rubin, Harvey
CORPORATE SOURCE: Dep. Dermatol., Univ. Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: J. Biol. Chem. (1989), 264(35), 21308-15
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ability of plasma proteinase **inhibitors** to inactivate human **chymase**, a chymotrypsin-like proteinase stored within mast cell secretory granules, was investigated. Incubation with plasma resulted in >80% inhibition of **chymase** hydrolytic activity for small substrates, suggesting that **inhibitors** other than .alpha.2-macroglobulin were primarily responsible for **chymase** inactivation. Depletion of specific **inhibitors** from plasma by immunoadsorption using antisera against individual **inhibitors** established that .alpha.1-antichymotrypsin (.alpha.1-AC) and .alpha.1-proteinase **inhibitor** (.alpha.1-PI) were responsible for the inactivation. Characterization of the reaction between **chymase** and each **inhibitor** demonstrated in both cases the presence of 2 concurrent reactions proceeding at fixed relative rates. One reaction, which led to **inhibitor** inactivation, was .apprx.3.5 and 4.0-fold faster than the other, which led to **chymase** inactivation. This was demonstrated in linear titrns. of proteinase activity which exhibited end-point stoichiometries of 4.5 (.alpha.1-AC) and 5.0 (.alpha.1-PI) instead of unity, and SDS gels of reaction products which exhibited a banding pattern indicative of both an SDS-stable proteinase-**inhibitor** complex and 2 lower Mr **inhibitor** degrdn. products which appear to have formed by hydrolysis within the reactive loop of each **inhibitor**. At **inhibitor** concns. approaching those in plasma where **inhibitor**-to-**chymase** concn. ratios were in far excess of 4.5 and 5.0, the rate of **chymase** inactivation by both serpin **inhibitors** appeared to follow pseudo-first order kinetics. The apparent second order rate consts. of inactivation detd. from these data were .apprx.3000-fold lower than the rate consts. reported for human neutrophil cathepsin G and elastase with .alpha.1-AC and .alpha.1-PI, resp. This suggests that **chymase** would be inhibited

.apprx.650-fold more slowly than these proteinases when released into plasma. These studies demonstrate that although **chymase** is inactivated by serpin **inhibitors** of plasma, both **inhibitors** are better substrates for the proteinase than they are **inhibitors**. This finding along with the slow rates of inactivation indicates that regulation of human **chymase** activity may not be a primary function of plasma.

L13 ANSWER 60 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:20376 CAPLUS
DOCUMENT NUMBER: 110:20376
TITLE: Kunitz-type protease **inhibitor** found in rat mast cells. Purification, properties, and amino acid sequence
AUTHOR(S): Kido, Hiroshi; Yokogoshi, Yutaka; Katunuma, Nobuhiko
CORPORATE SOURCE: Inst. Enzyme Res., Univ. Tokushima, Tokushima, 770, Japan
SOURCE: J. Biol. Chem. (1988), 263(34), 18104-7
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A low-mol.-wt. serine protease **inhibitor**, named trypstatin, was purified from rat peritoneal mast cells. It was a single polypeptide with 61 amino acid residues and mol. wt. 6610. Trypstatin markedly inhibited **blood**-coagulation factor Xa (Ki = 1.2 .times. 10-10 M) and tryptase (Ki = 3.6 .times. 10-10 M) from rat mast cells, which have activities that convert prothrombin to thrombin. It also inhibited porcine pancreatic trypsin (Ki = 1.4 .times. 10-8 M) and **chymase** (Ki = 2.4 .times. 10-8 M) from rat mast cells, but not papain, thrombin, or porcine pancreatic elastase. Trypstatin formed a complex in a molar ratio of 1:1 with trypsin and 1 subunit of tryptase. The complete amino acid sequence of this **inhibitor** was detd. and compared with those of Kunitz-type **inhibitors**. Trypstatin had a high degree of sequence homol. with human and bovine inter-.alpha.-trypsin **inhibitors**, A4751 Alzheimer's disease amyloid protein precursor, and basic pancreatic trypsin **inhibitor**. However, unlike other known Kunitz-type protease **inhibitors**, it inhibited factor Xa most strongly.

L13 ANSWER 61 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:3847 CAPLUS
DOCUMENT NUMBER: 102:3847
TITLE: Circulating proalbumin associated with a variant proteinase **inhibitor**
AUTHOR(S): Brennan, Stephen O.; Owen, Maurice C.; Boswell, D. Ross; Lewis, Jessica H.; Carrell, Robin W.
CORPORATE SOURCE: Pathol. Dep., Christchurch Hosp., Christchurch, N. Z.
SOURCE: Biochim. Biophys. Acta (1984), 802(1), 24-8
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The unique finding of normal proalbumin in human plasma provides an insight into the mechanism of propeptide cleavage. Proalbumin, present as 1-5% of the total albumin, was found in a boy whose prime problem was the presence of a mutant proteinase **inhibitor**, .alpha.1-antitrypsin Pittsburgh (methionine-358 .fwdarw. arginine) (Owen, M.C., et al., 1983). The inferred structure of human proalbumin was confirmed as Arg-Gly-Val-Phe-Arg-Arg-albumin. Of various enzymes (trypsin, mast cell tryptase, thrombin, chymotrypsin, mast cell **chymase**, and cathepsin B), only trypsin was capable of converting proalbumin to albumin. There was no conversion when proalbumin was incubated with whole **blood**, plasma, or serum. However, i.v. injection of proalbumin into a rat resulted in complete conversion to albumin, the half-life of

this process being 6 h. Thus, propeptide cleavage is dependent on a serine proteinase which is inhibited intracellularly by the mutant **inhibitor**. All the albumin in the boy was secreted as proalbumin, but was subjected to a sep. cleavage process after export from the hepatocyte.

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     FILE 'REGISTRY' ENTERED AT 16:56:52 ON 02 SEP 2002
L1              STRUCTURE UPLOADED
L2           19 S L1
L3          218 S L1 FUL

     FILE 'CAPLUS' ENTERED AT 16:57:28 ON 02 SEP 2002
L4          385 S CHYMASE AND INHIBITOR?
L5      1203367 S VASCULAR OR LIPID OR BLOOD
L6        55122 S ARTERIOSCLEROSIS OR CORONARY OR ANGIOPLASTY OR CLAUDICATION
L7        59714 S (CEREBRAL INFARCTION) OR ANEURYSM OR GANGRENE OR HYPERTENSION
L8           51 S RENAL INFARCTION
L9      1249143 S L5 OR L6 OR L7 OR L8
L10         120 S L4 AND L9
L11           8 S L3
L12         117 S L10 NOT L11
L13          61 S L12 NOT PY>1999

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